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Stereochemical evaluation of bis(phosphine) copper catalysts for the asymmetric alkylation of 3-bromooxindoles with α -arylated malonate esters

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Abstract

An improved method for the asymmetric alkylation of 3-bromooxindoles with α -arylated malonate esters is described. The asymmetric alkylation demonstrated was achieved up to 70% ee utilizing a copper(II) bis(phosphine) complex.

Keywords

3,3-Disubstituted oxindole; Chiral bis(phosphine) ligands; Copper catalysis; Asymmetric catalysis

1. Introduction

3,3-Disubstituted oxindole moieties are present in a wide variety of natural products and pharmaceutical agents.¹ Accordingly, methods for the asymmetric construction of 3,3-disubstituted oxindoles have attracted considerable attention from the synthetic community, and a number of catalytic stereoselective approaches to provide C3 quaternary stereocenters on oxindoles have been reported.^{2,3} In 2007, we discovered that 3,3-disubstituted oxindoles **3** were furnished efficiently by base-mediated alkylation of reactive electrophilic *o*-azaxylylene **2**, generated from 3-halo-oxindole **1**, with nucleophilic malonate esters (Scheme 1a).^{4a} Additionally, we developed a method for the stereoselective alkylation of 3-bromooxindoles by using a copper (*R*)-Ph-BOX ligand complex (Scheme 1b).^{4b}

Following our development of these methods, our attention turned to the syntheses of the polycyclic alkaloids communesin F and perophoramidine.^{5,6} We envisioned that the

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

stereochemistry at the vicinal quaternary centers on communesin F and perophoramidine could be installed utilizing the conditions described in Scheme 1b. However, attempts to produce diesters **8** and **9** via copper(II) bisoxazoline catalyzed enantioselective alkylation of 3-bromooxindoles **4** and **5** with α -arylated malonate esters **6** and **7** were unsuccessful (Scheme 2). Perhaps this result was to be expected, since the nucleophiles (α -arylated malonate esters **6** and **7**) were both sterically demanding and electronically deactivated by resonance stabilization through the *o*-nitrophenyl substituent. Therefore, we pursued the development of an alternative catalytic system.

In our previous studies, we tested a variety of metal catalysts (e.g. Cu^{II}, Mg^{II}, La^{III}, and Ni^{II}) and discovered that the combination of Cu^{II} and a chiral bisoxazoline ligand effectively promoted the catalytic reaction.⁴ Chiral Cu(II) bis(phosphine) complexes have also found use in stereoselective synthesis.⁷ Since the catalytic system can be formed with a number of different chiral bis(phosphine) ligands, quite a few options would be available for developing a stereoselective reaction. Herein, we describe several screening studies designed and undertaken to optimize the reaction conditions for the alkylation of 3-bromooxindoles with α -arylated malonate esters using a copper(II) bis(phosphine) catalyst.

2. Results and discussion

2.1. Initial screening results

To develop a stereoselective alkylation method, we chose simple substrates for optimization studies; specifically, we used bromooxindole **5** without a substituent on the aromatic ring and *o*-nitrophenyl dimethylmalonate **12** as a coupling partner. Bromooxindole **5** was easily prepared from indole in four steps by a known sequence,⁵ which was then added to *o*-nitrophenyl dimethylmalonate **12** and cesium carbonate in THF solvent to afford a racemic product **13** in good yield. (Scheme 3).

Choosing (*R*)-BINAP as a chiral ligand, we began our research by screening various copper sources, bases, and solvents. For instance we attempted the following variations of copper ions: Copper(II) triflate, copper(II) chloride with silver hexafluoroantimonate, copper(II) isobutyrate, copper(II) *tert*-butoxide (generated in situ by adding lithium *tert*-butoxide to copper(II) isobutyrate and ligand mixture), copper(II) ethylhexanoate, and copper(II) trifluoroacetylacetonate. We explored both organic and inorganic bases, including diisopropylethylamine, pyridine, tetramethylethylenediamine (TMEDA), triethylamine, diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), sodium carbonate, potassium acetate, sodium ethylhexanoate and cesium carbonate. The various reactions combinations were attempted in the following solvents: dichloromethane, tetrahydrofuran, benzene, acetonitrile, and dioxane. Evaluating the 93 reactions that were explored,⁸ we found that copper(II) *tert*-butoxide and the ligand complex generated in THF, which was similar to Fandrick's conditions for asymmetric propargylation,⁷ exhibited the best reactivity without generation of side products for the coupling of the arylated malonate **12** and bromooxindole **5** in CH₂Cl₂ (high conversion, 20% ee).

2.2. Ligand screening and optimization studies

Based on previous studies, we selected copper(II) isobutyrate, lithium *tert*-butoxide and THF solvent for generation of the catalytic species with chiral ligands, diisopropylamine as the base and CH₂Cl₂ as solvent. We have screened 69 chiral bis(phosphine) ligands⁸ under similar condition, finding WALPHOS and DiazaPHOS to give the best enantioselectivities (Figure 1).

Having identified the most effective ligands, we next screened several copper sources under lower temperatures. Although none of these sources exhibited better results than the combination of copper(II) isobutyrate and lithium *tert*-butoxide for WALPHOS (**N1** and **N2**), we were able to observe better stereoselectivity at low temperature (Table 1, entries 6 and 16). With DiazaPHOS (**W1**), copper(II) triflate showed better selectivity at 0 °C (Table 1, entries 22 and 23).

With a suitable bis(phosphine) ligand in hand (**N1**), we tested multiple solvents and bases. However, amine bases weaker than Hünig's base (Table 2, entries 1-12) could not initiate the reaction, whereas stronger base (entries 13-18) decreased the stereoselectivity. The copper bis(phosphine) complex demonstrated similar selectivity in dichloromethane (entry 19), THF (entry 20), and chloroform (entry 22), however it showed worse selectivity in acetonitrile (entry 21) and failed to proceed at all in toluene and 1,2-dimethoxyethane (DME).

In addition to these studies, we examined the effect of the catalyst and ligand loading on the stereoselectivity of our alkylation reaction. Unsatisfactory results were produced with low catalyst or ligand loading (Table 3, entries 1,2 and 4), but 20 mol % of copper(II) isobutyrate and 40 mol % of the ligand gave the product in 56% ee (Table 3, entry 3). Stoichiometric amounts of the copper precursor and ligand produced only a slight increase in ee (Table 3, entry 5). Additionally, we investigated the impact of the equivalents of Hünig's base on the selectivity of the reaction. Results showed the amount of Hünig's base had little effect on the stereoselectivity of the product (Table 3, entries 6-13). Subsequent examination of concentration effects showed lowering the concentration of the reaction mixture from 0.05 M to 0.02 M resulted in increase stereoselectivity (Table 4).

Finally, we explored a set of WALPHOS ligands (**N1** – **N8**) under our optimized conditions. Gratifyingly, we observed improved ee by using (Ph,Cy)-WALPHOS (Table 5, entry 5), leading to product formation in 70% ee with moderate conversion, whereas other ligands showed diminished selectivity. To date, this is the best result we have, which is a great improvement over the starting point.

3. Conclusion

Asymmetric alkylation of 3-haloindoles with malonate esters is an effective method to construct 3,3,-disubstituted oxindole moieties. Herein, we have reported that copper(II) chiral bis(phosphine) complex demonstrated reactivity with a highly stabilized and sterically hindered α -arylated malonate ester, which were unreactive substrates in previously developed conditions. This method could be applied to the installation of vicinal quaternary

centers on the communesin F and perophoramidine scaffolds and could be useful in the synthesis of a variety of other natural products.

4. Selected experimentals

4.1. Synthesis of *rac*-**13**

To a flame-dried round-bottomed flask equipped with a stirbar, was added bromooxindole **5** (20 mg, 0.045 mmol), *o*-nitrophenyl dimethylmalonate **12** (37 mg, 0.135 mmol) and THF (0.5 mL). To the mixture was added cesium carbonate (47.4 mg, 0.045 mmol) at ambient temperature and the reaction mixture was then stirred for 3 hr. The reaction mixture was then treated with saturated NH₄Cl aqueous solution, extracted with EtOAc, washed with brine and dried over MgSO₄. After concentration *in vacuo*, the crude product was obtained. Chromatography (6:1 hexanes: ethyl acetate) on silica gel afforded the title compound **13** (23 mg, 80% yield) as colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 8.0 (d, *J* = 8.1 Hz, 1H), 7.85 (s, 1H), 7.74 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.40 (dtd, *J* = 26.6, 7.4, 1.5 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.14 (td, *J* = 7.7, 1.3 Hz, 1H), 6.90 (td, *J* = 7.7, 1.2 Hz, 1H), 6.75 (dd, *J* = 7.8, 1.1 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.35 (ddd, *J* = 9.5, 8.4, 6.9 Hz, 1H), 3.06 (td, *J* = 9.3, 4.5, 1H), 2.93 (ddd, *J* = 12.6, 8.8, 6.7 Hz, 1H), 2.54 (ddd, *J* = 12.8, 8.4, 4.4 Hz, 1H), 0.89 (s, 21H). ¹³C NMR (126 MHz, CDCl₃) δ 177.86, 167.63, 167.27, 150.34, 140.67, 132.46, 131.12, 129.49, 129.23, 128.63, 128.61, 126.73, 125.39, 122.45, 109.98, 109.12, 59.52, 56.71, 52.81, 52.80, 38.34, 29.70, 17.85, 17.84, 11.80. IR (Neat Film, NaCl) 2923, 2852, 1722, 1617, 1532, 1463, 1353, 1259, 1097, 992, 799, 753 cm⁻¹; HRMS (MM) *m/z* calc'd for C₃₀H₄₀N₂O₈Si [M+H]⁺: 585.2627, found 585.2636.

4.2. Ligand Screening procedure

Every step was performed in a nitrogen-filled glove box. Solutions of copper(II) isobutyrate (8 mg, 0.034 mmol) in THF (3.5 mL), lithium *tert*-butoxide (2.72 mg, 0.034 mmol) in THF (3.5 mL), bromooxindole **5** (70 mg, 0.17 mmol) and malonate **12** (129 mg, 0.51 mmol) in CH₂Cl₂ (1.75 mL), *i*-Pr₂NEt (0.1 mL, 0.57 mmol) in CH₂Cl₂ (2 mL) were prepared in 2 dram vials prior to reaction setup. To 1 dram vials equipped with stirbars, and ligand (1.1 μmol, 22 mol %) were distributed copper(II) isobutyrate in THF (0.1 mL, 0.97 μmol, 20 mol %). The heterogeneous solution was agitated at room temperature for 10-20 min until a clear homogeneous solution was generated. The reaction mixtures were charged with lithium *tert*-butoxide in THF (0.1 mL, 0.97 μmol, 20 mol %). Reaction mixtures were allowed to stir for 5 min and concentrated under reduced pressure. A mixture of bromooxindole **5** and malonate **12** in CH₂Cl₂ (0.05 mL, 4.85 μmol, 14.55 μmol) was dispensed to each vial and allowed to stir for 10 min. After setting the reaction temperature, *i*-Pr₂NEt in CH₂Cl₂ (0.05 mL, 14.55 μmol, 3 equiv) was added to the reaction vials and allowed to stir for 48 h. Upon completion, sat. aq. ammonium chloride solution (0.1 mL) was added, and the mixture was filtered through silica gel. Each filtrate was diluted by 1 mL of solvent (ethyl acetate or isopropanol) and analyzed by chiral SFC. The mixture was separated by an AD-H column with 20% isopropanol as eluent. See supplementary material for more details.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. See supplementary material for the list of chiral bis(phosphine) ligands and screening results.

Figure 1.
Results with DiazaPHOS and WALPHOS

Scheme 1.

Construction of 3,3-disubstituted oxindoles by alkylation of 3-halo-oxindoles.

Scheme 2.

Attempts for alkylation of 3-bromooxindoles with α -arylated malonate esters.

Scheme 3.
Synthesis of the racemic product.

Table 1

Further investigations using WALPHOS and DiazaPHOS in the alkylation reaction.

Entry	Metal Sources	Ligand	Additive	Temp.	ee ^a
1	CuCl ₂	N1	AgBF ₄	−45 °C	–
2	CuCl ₂	N1	AgNTf ₂	−45 °C	–
3	CuCl ₂	N1	AgPF ₆	−45 °C	–
4	CuCl ₂	N1	AgSbF ₆	−45 °C	–
5	CuCl ₂	N1	LiOt-Bu	−45 °C	–
6	Cu(isobutyrate) ₂	N1	LiOt-Bu	−45 °C	44%
7	Cu(isobutyrate) ₂	N1	AgSbF ₆	−45 °C	–
8	Cu(hfacac) ₂	N1		−45 °C	trace
9	Cu(OTf) ₂	N1		−45 °C	trace
10	Cu(OTf) ₂	N1	LiOt-Bu	−45 °C	23%
11	Cu(EH) ₂	N1		−45 °C	trace
12	CuCl ₂	N2	AgBF ₄	−45 °C	–
13	CuCl ₂	N2	AgNTf ₂	−45 °C	–
14	CuCl ₂	N2	AgPF ₆	−45 °C	–
15	CuCl ₂	N2	AgSbF ₆	−45 °C	–
16	Cu(isobutyrate) ₂	N2	LiOt-Bu	−45 °C	54%
17	Cu(hfacac) ₂	N2		−45 °C	30%
18	Cu(OTf) ₂	N2		−45 °C	45%
19	Cu(EH) ₂	N2		−45 °C	trace
20	Cu(isobutyrate) ₂	W1	LiOt-Bu	0 °C	trace
21	Cu(isobutyrate) ₂	W1 ^b	LiOt-Bu	0 °C	trace
22	Cu(OTf) ₂	W1		0 °C	40%
23	Cu(OTf) ₂	W1 ^b		0 °C	50%

Conditions: 0.0049 mmol **5**, 0.0145 mmol **12**, Cu (20 mol %), Ligand (22 mol %), Additive (20 mol %), *i*-Pr₂NEt (3 equiv.), 0.1 mL CH₂Cl₂ (0.049 M). Metal catalyst, ligand and additives were mixed in THF. THF was removed *in vacuo*, and the resultant was diluted with the reaction solvent. The reaction was initiated by addition of base. Cu(hfacac)₂: copper(II) hexafluoroacetylacetonate, Cu(EH)₂: copper(II) ethylhexanoate.

–: Desired product was not observed.

^a enantiomeric excess was measured by chiral SFC.

^b 44 mol % of ligand was used.

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Table 2

Investigation of reaction solvents and bases with WALPHOS in the alkylation reaction.

Entry	Solvent	Base	ee
1	CH ₂ Cl ₂	DABCO	–
2	THF	DABCO	–
3	CH ₃ CN	DABCO	–
4	CHCl ₃	DABCO	–
5	Toluene	DABCO	–
6	DME	DABCO	–
7	CH ₂ Cl ₂	DMAP	–
8	THF	DMAP	–
9	CH ₃ CN	DMAP	–
10	CHCl ₃	DMAP	–
11	Toluene	DMAP	–
12	DME	DMAP	–
13	CH ₂ Cl ₂	Cs ₂ CO ₃	35%
14	THF	Cs ₂ CO ₃	15%
15	CH ₃ CN	Cs ₂ CO ₃	20%
16	CHCl ₃	Cs ₂ CO ₃	20%
17	Toluene	Cs ₂ CO ₃	–
18	DME	Cs ₂ CO ₃	10%
19	CH ₂ Cl ₂	<i>i</i> -Pr ₂ NEt	40%
20	THF	<i>i</i> -Pr ₂ NEt	50%
21	CH ₃ CN	<i>i</i> -Pr ₂ NEt	30%
22	CHCl ₃	<i>i</i> -Pr ₂ NEt	40%
23	Toluene	<i>i</i> -Pr ₂ NEt	–
24	DME	<i>i</i> -Pr ₂ NEt	–

Conditions: 0.0024 mmol **5**, 0.0072 mmol **12**, Cu (20 mol %), Ligand (22 mol %), LiOt-Bu (20 mol %), Base (3 equiv), 0.06 mL Solvent (0.04 M).

–: Desired product was not observed.

Table 3

Examination of the amount of catalyst and ligand loading in the alkylation reaction.

Entry	Cu(isobutyrate)_2	Ligand	$i\text{-Pr}_2\text{NEt}$	ee
1	10 mol %	10 mol %	3.0 equiv	25%
2	10 mol %	20 mol %	3.0 equiv	28%
3	20 mol %	40 mol %	3.0 equiv	56%
4	20 mol %	10 mol %	3.0 equiv	35%
5	1 equiv	1 equiv	3.0 equiv	60%
6	20 mol %	20 mol %	1.0 equiv	33%
7	20 mol %	20 mol %	1.5 equiv	35%
8	20 mol %	20 mol %	2.0 equiv	38%
9	20 mol %	20 mol %	2.5 equiv	37%
10	20 mol %	20 mol %	4.0 equiv	36%
11	20 mol %	20 mol %	5.0 equiv	37%
12	20 mol %	20 mol %	6.0 equiv	36%
13	20 mol %	20 mol %	20 equiv	36%

Conditions: 0.0049 mmol **5**, 0.0145 mmol **12**, LiOt-Bu (10 mol %), 0.1 mL CH_2Cl_2 (0.049 M).

Table 4

Examination of concentration in the malonate addition reaction.

Entry	Concentration	ee
1	0.005 M	53%
2	0.01 M	63%
3	0.02 M	64%
4	0.05 M	55%
5	0.25 M	40%

Conditions: 0.0049 mmol **5**, 0.0145 mmol **13**, Cu (20 mol %), Ligand (40 mol %), LiOt-Bu (20 mol %), *i*-Pr₂NEt (3 equiv).

Table 5

The effect of WALPHOS substituents under optimized condition in the alkylation reaction.

Entry	Ligand	ee
1	N1	60%
2	N2	trace
3	N3	25%
4	N4	25%
5	N5	70%
6	N6	—
7	N7	—
8	N8	—

Conditions: 0.0049 mmol **5**, 0.0145 mmol **12**, Cu (20 mol %), Ligand (40 mol %), LiOt-Bu (20 mol %), $i\text{-Pr}_2\text{NEt}$ (3 equiv), 0.25 mL CH_2Cl_2 (0.02 M).

—: Desired product was not observed.