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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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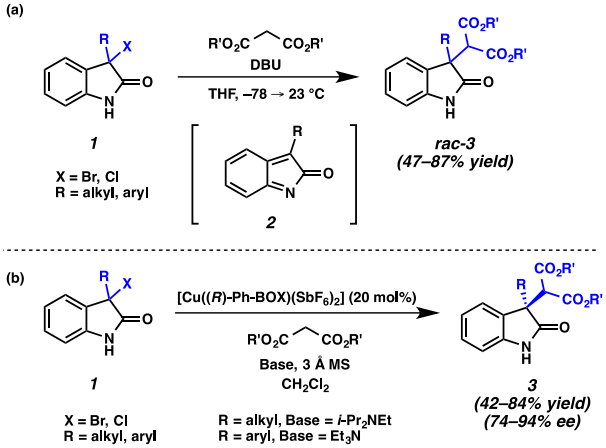
ABSTRACT

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.

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*-azaxylyxene **2**, generated from 3-halooxindole **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 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.



Scheme 1. Construction of 3,3-disubstituted oxindoles by alkylation of 3-halooxindoles.

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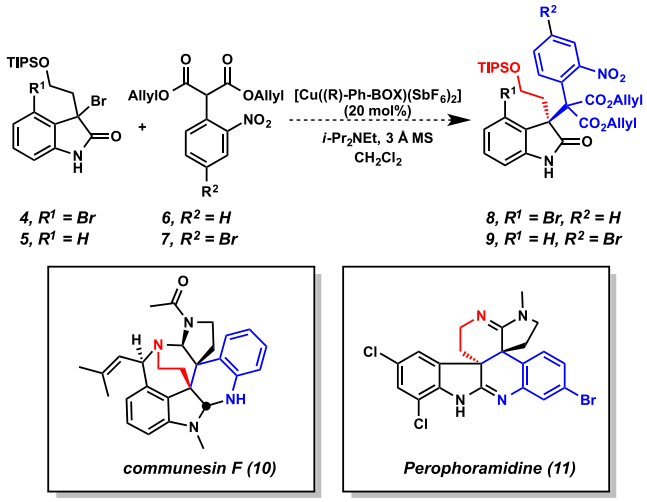


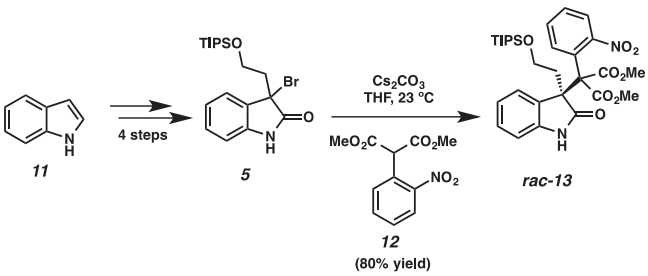
Scheme 2. Attempts for alkylation of 3-bromooxindoles with α-arylated malonate esters.

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).



Scheme 3. Synthesis of the racemic product.

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 reaction 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 CH_2Cl_2 (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 CH_2Cl_2 as solvent. We have screened 69 chiral bis(phosphine) ligands[8] under similar condition, finding WALPHOS and DiazaPHOS to give the best enantioselectivities (Fig. 1).

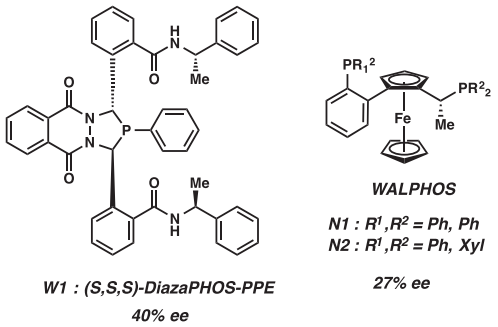
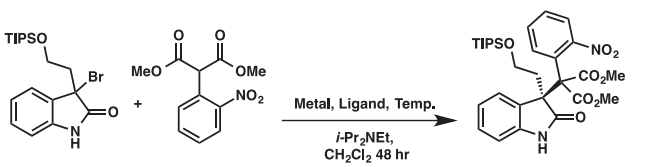


Fig. 1. Results with DiazaPHOS and WALPHOS.

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).

Table 1
Further investigations using WALPHOS and DiazaPHOS in the alkylation reaction



Entry	Metal sources	Ligand	Additive	Temp (°C)	ee[a] (%)
1	$CuCl_2$	**N1**	$AgBF_4$	−45	—
2	$CuCl_2$	**N1**	$AgNTf_2$	−45	—
3	$CuCl_2$	**N1**	$AgPF_6$	−45	—
4	$CuCl_2$	**N1**	$AgSbF_6$	−45	—
5	$CuCl_2$	**N1**	LiO*t*-Bu	−45	—
6	$Cu(isobutyrate)_2$	**N1**	LiO*t*-Bu	−45	44
7	$Cu(isobutyrate)_2$	**N1**	$AgSbF_6$	−45	—
8	$Cu(hfacac)_2$	**N1**		−45	Trace
9	$Cu(OTf)_2$	**N1**		−45	Trace
10	$Cu(OTf)_2$	**N1**	LiO*t*-Bu	−45	23
11	$Cu(EH)_2$	**N1**		−45	Trace

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Table 1 (*continued*)

Entry	Metal sources	Ligand	Additive	Temp (°C)	ee[a] (%)
12	$CuCl_2$	**N2**	$AgBF_4$	−45	—
13	$CuCl_2$	**N2**	$AgNTf_2$	−45	—
14	$CuCl_2$	**N2**	$AgPF_6$	−45	—
15	$CuCl_2$	**N2**	$AgSbF_6$	−45	—
16	Cu(isobutyrate)$_2$	**N2**	LiO*t*-Bu	−45	54
17	Cu(hfacac)$_2$	**N2**		−45	30
18	Cu(OTf)$_2$	**N2**		−45	45
19	Cu(EH)$_2$	**N2**		−45	Trace
20	Cu(isobutyrate)$_2$	**W1**	LiO*t*-Bu	0	Trace
21	Cu(isobutyrate)$_2$	**W1**[b]	LiO*t*-Bu	0	Trace
22	Cu(OTf)$_2$	**W1**		0	40
23	Cu(OTf)$_2$	**W1**[b]		0	50

Conditions: 0.0049 mmol **5**, 0.0145 mmol **12**, Cu (20 mol %), ligand (22 mol %), sdditive (20 mol %), *i*-Pr_2NEt (3 equiv), 0.1 mL CH_2Cl_2 (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.

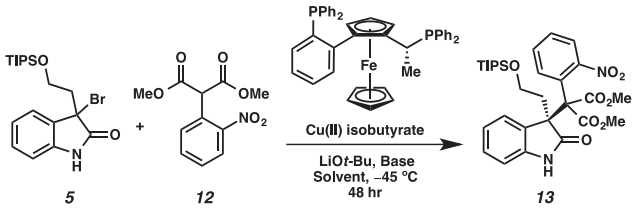
[a] Enantiomeric excess was measured by chiral SFC. —: Desired product was not observed.

[b] Ligand of 44 mol % was used.

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 of stereoselectivity (Table 4).

Table 2
Investigation of reaction solvents and bases with WALPHOS in the alkylation reaction

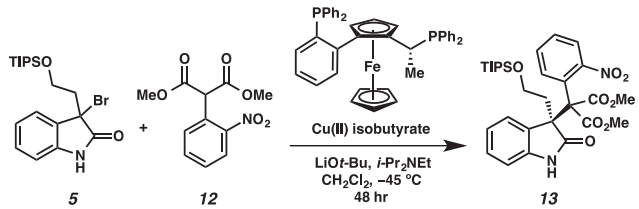


5 12 13

Entry	Solvent	Base	ee (%)
1	CH_2Cl_2	DABCO	—
2	THF	DABCO	—
3	CH_3CN	DABCO	—
4	$CHCl_3$	DABCO	—
5	Toluene	DABCO	—
6	DME	DABCO	—
7	CH_2Cl_2	DMAP	—
8	THF	DMAP	—
9	CH_3CN	DMAP	—
10	$CHCl_3$	DMAP	—
11	Toluene	DMAP	—
12	DME	DMAP	—
13	CH_2Cl_2	Cs_2CO_3	35
14	THF	Cs_2CO_3	15
15	CH_3CN	Cs_2CO_3	20
16	$CHCl_3$	Cs_2CO_3	20
17	Toluene	Cs_2CO_3	—
18	DME	Cs_2CO_3	10
19	CH_2Cl_2	*i*-Pr_2NEt	40
20	THF	*i*-Pr_2NEt	50
21	CH_3CN	*i*-Pr_2NEt	30
22	$CHCl_3$	*i*-Pr_2NEt	40
23	Toluene	*i*-Pr_2NEt	—
24	DME	*i*-Pr_2NEt	—

Conditions: 0.0024 mmol **5**, 0.0072 mmol **12**, Cu (20 mol %), ligand (22 mol %), LiO*t*-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

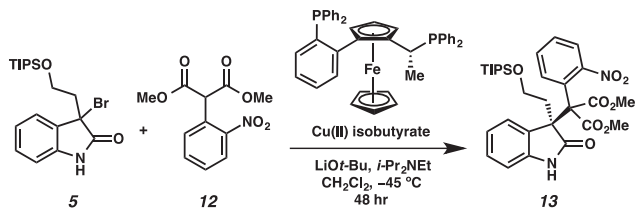


5 12 13

Entry	Cu(isobutyrate)$_2$	Ligand	*i*-Pr_2NEt (equiv)	ee (%)
1	10 mol %	10 mol %	3.0	25
2	10 mol %	20 mol %	3.0	28
3	20 mol %	40 mol %	3.0	56
4	20 mol %	10 mol %	3.0	35
5	1 equiv	1 equiv	3.0	60
6	20 mol %	20 mol %	1.0	33
7	20 mol %	20 mol %	1.5	35
8	20 mol %	20 mol %	2.0	38
9	20 mol %	20 mol %	2.5	37
10	20 mol %	20 mol %	4.0	36
11	20 mol %	20 mol %	5.0	37
12	20 mol %	20 mol %	6.0	36
13	20 mol %	20 mol %	20	36

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

Table 4
Examination of concentration in the malonate addition reaction



5 12 13

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

Conditions: 0.0049 mmol **5**, 0.0145 mmol **13**, Cu (20 mol %), ligand (40 mol %), LiO*t*-Bu (20 mol %), *i*-Pr_2NEt (3 equiv).

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

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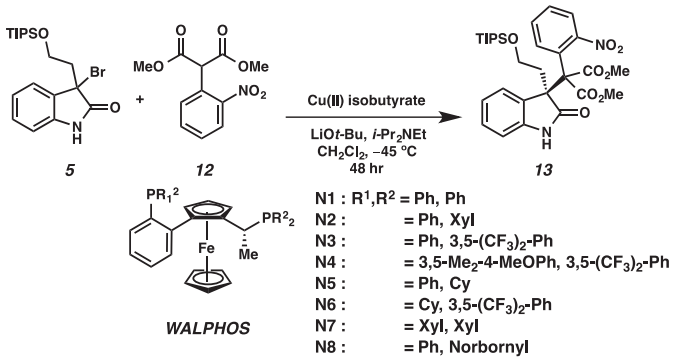
Table 5
The effect of WALPHOS substituents under optimized condition in the alkylation reaction



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 %), LiO*t*-Bu (20 mol %), *i*-Pr_2NEt (3 equiv), 0.25 mL CH_2Cl_2 (0.02 M). —: Desired product was not observed.

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-halooxindoles 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 stir-bar were 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 h. The reaction mixture was then treated with saturated NH_4Cl aqueous solution, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. 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, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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 calcd for $C_{30}H_{40}N_2O_8Si$ $[M+H]^+$: 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 CH_2Cl_2 (1.75 mL), *i*-Pr_2NEt (0.1 mL, 0.57 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (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*-Pr_2NEt in CH_2Cl_2 (0.05 mL, 14.55 μmol, 3 equiv) was added to the reaction vials and allowed to stir for 48 h. Upon completion, saturated aqueous 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 eluant. See Supplementary data for more details.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.10.065.

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

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