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Cu(II)-^{t}Bu-PHOX Catalyzed Enantioselective Malonate Addition onto 3-Hydroxy 2-Oxindoles: Application in the Synthesis of Dimeric Pyrroloindoline Alkaloids*

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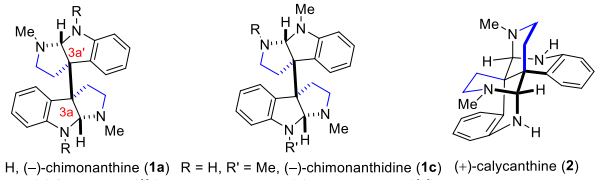
K. Naresh Babu,[a] Lakshmana K. Kinthada,[a] Partha Pratim Das,[b] and Alakesh Bisai*[a]

Abstract. An efficient Cu(II)-PHOX-catalyzed malonate addition onto 3-hydroxy 3-indolyl-2-oxindoles is envisioned to afford excellent enantioselectivities (up to >99% ee) in high chemical yields. A detailed characterization data including X-ray, NMR, CV and EPR experiments suggest that a Cu(II)-complex is involved as an active species in this process. Applying the strategy, an advanced intermediate of cyclotryptamine alkaloids has been synthesized in few steps addressing a general approach to bis-cyclotryptamine alkaloids.

All-carbon quaternary stereocenter bearing pyrroloindolines is a common structural feature of a number of indole alkaloids.[1,2] Further, the dimeric cyclotryptamine alkaloids sharing vicinal all-carbon quaternary stereocentres, with a labile C_{3a}–$C_{3a'}$ σ-bond (Figure 1), remain one of the most fascinating targets which continues to attract tremendous synthetic interest (**1**-**2**, Figure 1).[3,4] Owing to their impressive biological activities,[5] there is an increased demand for the development of novel asymmetric strategies for their syntheses. Literature reported asymmetric strategies include Overman's elegant asymmetric approach using dialkylation or double Heck cyclizations to establish the quaternary stereocentres,[6] Movassaghi's expeditious Co(I)-promoted reductive homodimerization[7,8] as well as heterodimerization[9] reactions, and a related homodimerization strategy by Sodeoka.[10]

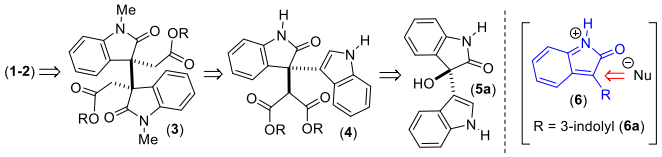


R = H, (–)-chimonanthine (**1a**) R = H, R' = Me, (–)-chimonanthidine (**1c**) (+)-calycanthine (**2**)
R = Me, (–)-folicanthine (**1b**) R = Me, R' = H, (–)-calycanthidine (**1d**)

Figure 1. Selected bis-cyclotryptamine alkaloids **1** and **2**.

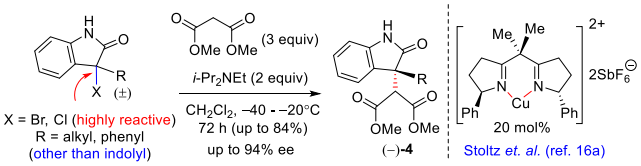
On the other hand, catalytic asymmetric approaches include enantioselective substitution of 3-hydroxy-2-oxindole with an enecarbamate by Gong;[11] Michael addition of indole to isatylidene-3-acetaldehyde by Zhang,[12] Michael reaction of *N*-Boc-protected bisoxindole with nitroethylene by Kanai and Matsunaga,[13] sequential Pd-catalyzed two-fold decarboxylative allylations by Trost[14] and the report by our group.[15] Despite these elegant reports, there is a strong need to develop a catalytic enantioselective method allowing access to wide range of cyclotryptamine alkaloids. In this communication, we report Cu(II)-*t*Bu-PHOX catalyzed enantioselective malonate addition onto 3-hydroxy 2-oxindoles for a target oriented synthesis of bis-tryptamine alkaloids.

Our retrosynthetic strategy to synthesize the core structure of **1a-d** is shown in Scheme 1. We envisioned that bis-ester **3** could serve as an advanced intermediate for the total synthesis of a number of dimeric cyclotryptamine alkaloids. The bisester **3** could be obtained from compound **4**, which in turn could be accessed from catalytic enantioselective manolate addition onto 3-(3'-indolyl)-3-hydroxy-2-oxindole **5**. In fact, Stoltz *et. al.* reported that indol-2-ones of type **6**[16a] generated from a base promoted reaction of highly reactive 3-halo-2-oxindoles could be used as electrophiles in the construction of enantioenriched 3,3-disubstituted oxindoles.[16, 17] In this elegant report, 3-halo-2-oxindoles containing alkyl and aryl groups (other than an indole substitution) well tolerated in achieving optimum enantioselectivity (Scheme 2).[16e]



Scheme 1. Retrosynthetic analysis of **1** and our hypothesis.

However, utilizing an indole ring at C-3 position of 2-oxindole for malonate substitution would be considerable challenge because of its inherent reactivity, and that is worth testing. Herein, we envisioned that 3-(3'-indolyl)-3-hydroxy-2-oxindole could be a potential substrate for an efficient Lewis acid-catalyzed malonate substitution reaction at C-3 position of 2-oxindole.[17c]



Scheme 2. Cu(II)-catalyzed malonate addition by Stoltz et. al.

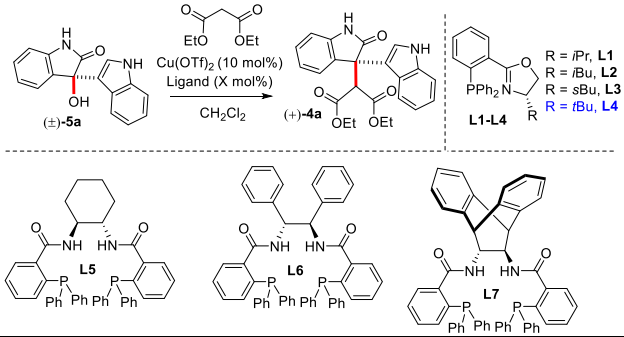
[a] *Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhauri, Bhopal – 462 066, Madhya Pradesh, India.*

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: Experimental procedures, additional reaction optimization, spectroscopic data for all new compounds.

At the outset, we selected 3-(3'-indolyl)-3-hydroxy-2-oxindole **5a** (1 equiv) and diethylmalonate (3 equiv) as the substrate and nucleophile for intial studies (Table 1). We have utilized a number of enantioenriched phosphine-oxazoline liagnds **L1-L4**[18] and C2-symmetric phosphine-carboxamide Trost ligands **L5-L7**[19] (Table 1). Initially, we found that 10 mol% $Cu(OTf)_2$ and 12 mol% ligands, *i*-PrPHOX (**L1**), *i*-BuPHOX (**L2**), *s*-BuPHOX (**L3**) and *t*-BuPHOX (**L4**) afforded product **4a** in 52% ee, 38% ee, 55% ee, and 72% ee, respectively, at room temperature (entries 1-4). The enantioselectivity was increased to 81% when the reaction was done at 0 ºC (entry 5). Interestingly, it was found that a Cu(II)-complex prepared from 10 mol% of Cu(II)OTf and 20 mol% *t*-BuPHOX (**L4**) in dichloromethane at 0 ºC afforded product **4a** in 92% ee and 84% isolated yield (entry 6).

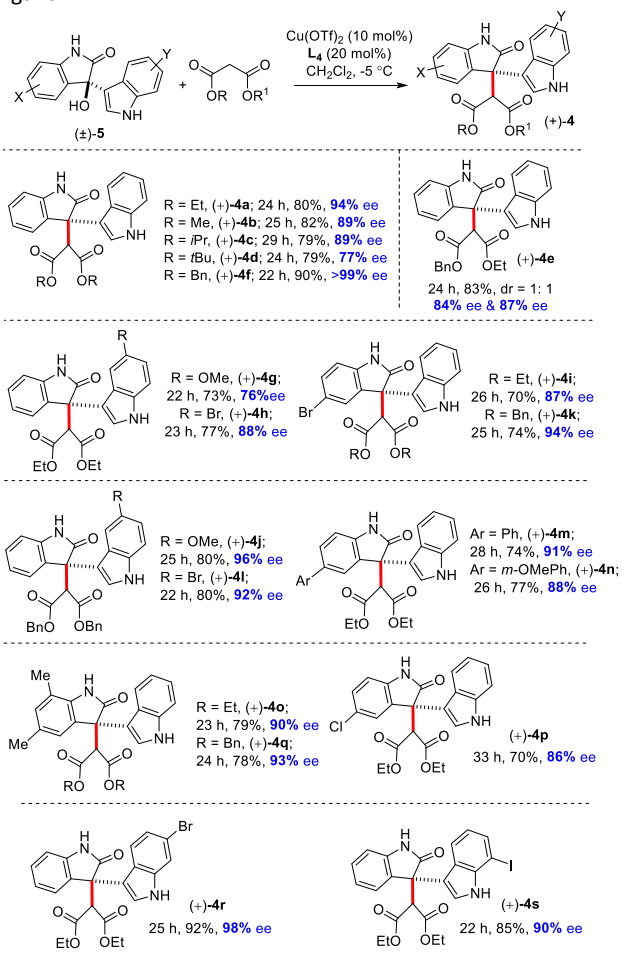
Table 1. Optimization of enantioselective malonate addition.[a, b]



entry	catalyst	ligand	temp.	time	% yield	% ee
1	$Cu(OTf)_2$	12 mol% **L1**	25 ºC	12 h	79%	52%
2	$Cu(OTf)_2$	12 mol% **L2**	25 ºC	13 h	80%	38%
3	$Cu(OTf)_2$	12 mol% **L3**	25 ºC	12 h	81%	55%
4	$Cu(OTf)_2$	12 mol% **L4**	25 ºC	13 h	84%	72%
5	$Cu(OTf)_2$	12 mol% **L4**	0 ºC	16 h	83%	82%
6	$Cu(OTf)_2$	20 mol% **L4**	0 ºC	15 h	84%	92%
7	$Cu(OTf)_2$	20 mol% **L5**	0 ºC	19 h	78%	24%
8	$Cu(OTf)_2$	20 mol% **L6**	0 ºC	19 h	72%	39%
9	$Cu(OTf)_2$	20 mol% **L7**	0 ºC	17 h	80%	40%
10	$In(OTf)_3$	20 mol% **L4**	0 ºC	15 h	20%	00%
11[c]	CuOTf	20 mol% **L4**	0 ºC	16 h	86%	83%
12	$Cu(OTf)_2$	20 mol% **L4**	-5 ºC	28 h	83%	94%
13	$Cu(OTf)_2$	20 mol% **L4**	-10 ºC	45 h	69%	88%

[a]all the reactions were carried out on a 0.08 mmol of **5a,** 0.23 mmol of diethylmalonate in 3 mL of dichloromethane in a screw capped vial. [b]Isolated yields. [c]10 mol% Cu(OTf).PhMe was used.

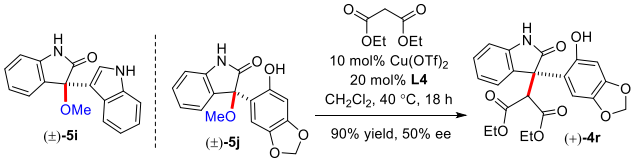
At 0 ºC, C_2-symmetric ligands **L5**, **L6**, and **L7** afforded **4a** in 24% ee, 39% ee, and 40% ee, respectively (entries 7-9). Other metal triflate such as $In(OTf)_3$ was not suitable for asymmetric induction (entry 10). It is interesting to note that, Cu(I)-**L4** complex also afforded **4a** 83% ee (entry 11). On further optimization, it was observed that product **4a** could be obtained in 94% ee and 88% ee, respectively, when the reaction was carried out at -5 ºC and -10 ºC (entries 12-13). Based on our exhaustive optimization, 10 mol% of Cu(II)OTf and 20 mol% *t*-BuPHOX (**L4**) in dichloromethane at -5 ºC was chosen as standard condition (entry 12). On examining the scope of this transformation, we found that malonates with different alkyl group have higher impact on enantioselectivity, clearly indicating sterics play crucial role on enantioselectivity (Scheme 2). Interestingly, it was observed that dibenzylmalonate can be added to (±)-**5a** via the *in situ* generated *o*-azaxylylene intermediate **6a**, to afford **4f** in >99% ee with 90% yield (Scheme 2). This is probably indicating that, the aryl moiety of benzylmalonate might be helping the transition state by its π-π stacking ability with phenyl ring of BuPHOX (**L4**) ligand.[20]



[a]all the reactions were carried out on 0.08 mmol of **5**, 0.23 mmol of dialylmalonate in 3 mL of CH_2Cl_2 in a screw capped vial in the presence of 0.008 mmol of Cu(II)OTf and 0.016 mmol of **L4**. [b]Isolated yields after column chromatography. [c]ee's were determined using chiral HPLC columns.

Scheme 3. Substrate scopes using various 3-hydroxy-2-oxindoles.

Further, we tested substrate scope using diethyl- and dibenzylmalonates under the optimized condition. As shown in Scheme 2, our optimized conditions could be extended to a variety of 3-(3'-indolyl)-3-hydroxy-2-oxindoles of type **5** with functionalization on both scaffolds namely 2-oxindole as well as indole part of **5**. As a result, a wide range of 3-(3'-indolyl)-3-malonyl-2-oxindoles bearing an all-carbon-quaternary centers at the pseudobenzylic position are obtained in good to excellent enantioselectivities with high yields (**4g-s**; Scheme 3).



Scheme 4. Effect of different 3-Methoxy-2-oxindoles.

Gratifyingly, malonate addition can also be done on 3-(3'-indolyl)-3-methoxy-2-oxindole **5i** to afford product **4a**, however, only up to 76% ee (-5 ºC, 26 h, 85% yield). Along similar lines, we also utilized 3-aryl-3-methoxy-2-oxindole **5j** which afforded product **4r** in 50%

ee, probably indicating that choice of aryl group also has important effect on enantioselectivty (Scheme 4).

To our notice, 3-hydroxy-2-oxindoles having alkyl functionalities such as **7a-d** didn't afford products under the optimized condition (Figure 2). In order to realize efficient reaction, an indole ring at C-3 position of 3-hydroxy 2-oxindole was required.[17c] These observations led us to postulate an alternative reactive intermediate **6b** (Mode 2, Figure 2) which might be responsible for efficient catalytic enantioselective malonate addition.[17c]

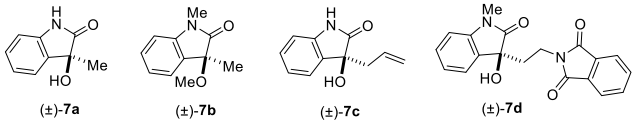


Figure 2. Substrates **7a-d** failed to afford product.

In case of aryl group having *o*-phenol moiety such as **5l**, it is most likely that malonate addition goes through intermediate **6c** (Figure 3). The observed lower enantioselectivity in case of **5l** (50% ee) could be attributed to speeding up the reverse reaction, where the presence of a free hydroxy group on the benzene ring stabilizes 'Mode 3' (see **6c**, Figure 3).[21b]

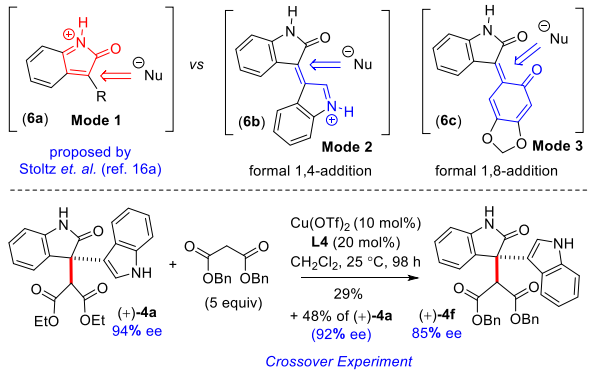


Figure 3. Plausible reactive intermediates and crossover experiment.

We also performed crossover experiments to check reversible nature of the catalytic enantioselective malonate addition (Figure 3). Reaction of (+)-**4a** (94% ee) with dibenzylmalonate in the presence of 20 mol% of Cu(II)-*t*-BuPHOX (**L4**) furnished enantioenriched (+)-**4f** (85% ee), clearly confirming the reversible nature of our methodology (Figure 3). Also, a reaction of (+)-**4a** (94% ee) with dibenzylmalonate in the presence of 20 mol% of Cu(II)OTf furnished (±)-**4f** in 85% yield at 25 ºC (98 h).

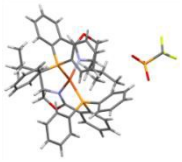


Figure 4. X-ray structure of 1:2 mixture $Cu(OTf)_2$ with **L2** (CCDC **1811398**).

Considering the fact that, present methodology works well with Cu(II) as well as Cu(I) (entries 11 and 12; Table 1), there is a possibility that copper can stabilize a distorted trigonal bipyramid (TBP) when coupled with ^{t}BuPHOX (**L4**), malonate, and intermediate **6b** (Figure 3). In fact, crystal of **L2** with Cu(II)OTf (Figure 4) clearly shows that a distorted TBP might be the geometry during the course of the reaction. Exhaustive studies (CV measurement, NMR studies, and EPR experiments) of Cu-complex of PHOX ligand suggests that a Cu(II)-**L2** is the active species for asymmetric malonate addition onto 3-hydroxy 2-oxindoles (see Supporting Information for detailed studies).

The stereochemistry rationale of Cu(II)-catalyzed malonate addition onto 3-hydroxy-2-oxindole is shown in Figure 5. In transition state I (**TS-I**), aryl group of **6b** (Mode 2) can be placed below to the oxazoline ring (sterically favored **TS**). In this favored model, the aryl group of α,β-unsaturated imine **6b** could orient itself in a manner so that it is orthogonal to one of the phenyl ring of -PPh_2 group (see favored **TS-I**). Thus, one of the phenyl rings on each oxazoline unit can attain a conformation to provide a suitable distance (~3.5 Å) from the aryl ring so as to provide stabilizing interactions.[20] Thus, the transition state becomes highly organized because of the stabilizing interactions, and the Cu(II)-malonate can approach to the electron-deficient α,β-unsaturated imine **6b** from '*Si*-face' (above face) leading to (*R*)-**4a**. Whereas, in transition state II (**TS-II**), aryl group of **6b** is placed below to phosphinyl group leading to severe steric repulsion with one of the phenyl groups of PPh_2 of ^{t}BuPHOX (**L4**), thereby, '*Re*-face' approach is retarded (see disfavored **TS-II**).[21a]

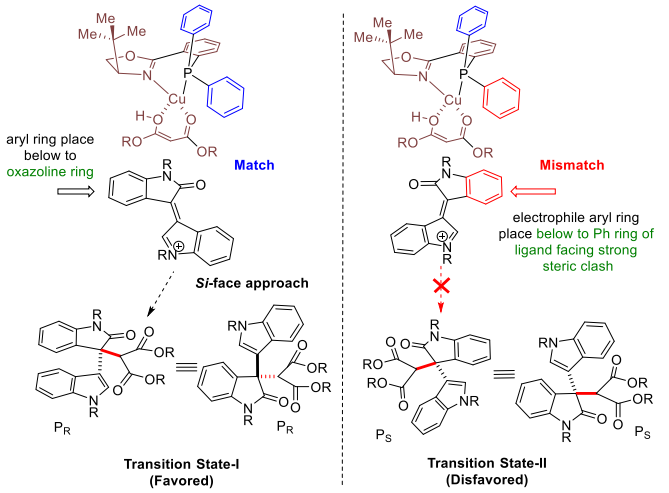
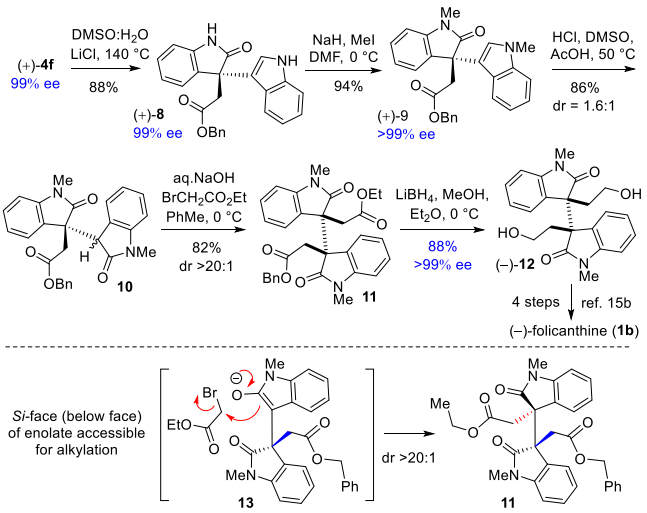


Figure 5. Rationale of stereochemistry.

We then proceeded to apply the new method for enantioselective synthesis of dimeric cyclotryptamine alkaloids sharing vicinal all-carbon quaternary stereocentres (Scheme 5). Thus, we began with 2-oxindole malonate adduct **4f** with 99% ee (Schemes 3).[22] Towards this, we carried out Krapcho decarboxylation of one of the esters functionality with LiCl at elevated temperature to form **8**, which was methylated to form **9** in 82% over 2 steps (Scheme 5). Later, indole functionality was converted to 2-oxindole by reaction with DMSO (HCl) in AcOH at 50 ºC to form **10** in 1.6:1 dr, which was then reacted with bromo ethylacetate to afford **11** in >20:1 dr. Excellent diastereoselectivity of alkylation using ethylbromoacetate can be attributed to *Si*-face approach of enolate **13**.[23] Compound **11** was reduced with $LiBH_4$ to form C_2-symmetric dimeric 2-oxindole **12** in 88% yield. Since, total synthesis of **1b** is known from diol, our effort culminated in formal total synthesis of (–)-folicanthine **1b** (Scheme 5).[15b]

In summary, we have developed a successful strategy for the construction of C3-quaternary 2-oxindoles containing an all-carbon quaternary stereocenters with high level of enantioselectivity by using a Cu(II)-catalyzed asymmetric alkylation reaction of 3-hydroxy-2-oxindoles with a variety of malonates. This stereoablative methodology involves the *in situ* formation of a highly reactive intermediate **6b** from 3-hydroxy-2-oxindoles

followed by enantioselective malonate addition. Utilizing aforementioned methodology, we have synthesized dimeric 2-oxindoles sharing vicinal all-carbon quaternary stereocentres in only 4 steps, which is structural feature of many naturally occurring alkaloids. Further investigation on mechanistic details and synthetic applications of our method are currently underway.



Scheme 5. Formal total synthesis of (–)-folicanthine **1b** and rationale of observe diastereoselectivity.

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(19) Trost Ligands **L5-L7**: (a) B. M. Trost, D. L. Van Vranken, *Angew. Chem., Int. Ed.* **1992**, *31*, 228. (b) B. M. Trost, D. A. Thaisrivongs, J. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 12439.

(20) For a review on the *p*-stacking effect in asymmetric synthesis, see: (a) G. B. Jones, B. J. Chapman, *Synthesis* **1995**, 475. (b) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.

(21) (a) Absolute configuration of malonate addition product was confirmed by transforming **4f** into known C_2-symmetric diol **12** (see, Scheme 4). (b) Reaction of **5a** with *t*-butyl acetoacetate and ethyl 2-oxo-cyclopentane carboxylate afforded racemic products clearly depicting the reversible nature of our process, which is relatively slow with malonates, but fast with the more acidic ketoesters (see, SI for details).

(22) The enantioselectivity of (+)-**4f** was found to be 98%, when the reaction was carried out in 0.25 g scale of 3-hydroxy 2-oxindole (0 ºC, 24 h, 83% yield). However, the enantioselectivity was dropped to 90%, when the reaction was performed on 0.5 g scale (0 ºC, 32 h, 79% yield).

(23) Alkylation from above face (*Re*-face) is retarded because of steric clash imposed by bulky benzylester group.

