C–H Activation

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Enantioselective Oxidative Cross-Coupling Reaction of 3-Indolylmethyl C–H Bonds with 1,3-Dicarbonyls Using a Chiral Lewis Acid-Bonded Nucleophile to Control Stereochemistry**

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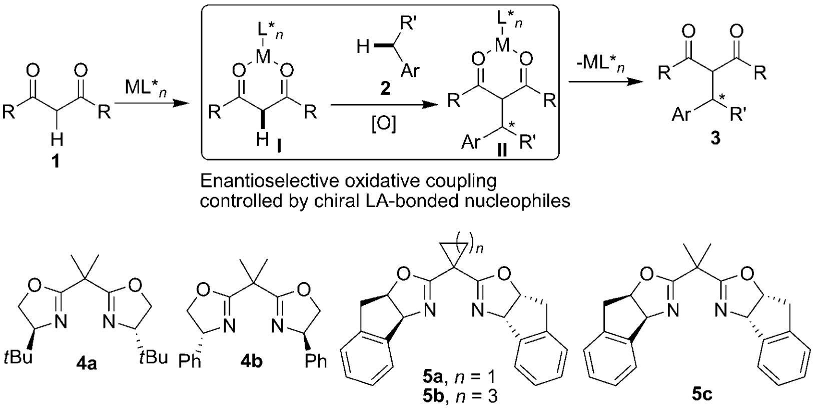
Dedicated to Professor You-Cheng Liu on the occasion of his 90th birthday

Cross-coupling reactions using C–H activation have emerged as robust alternatives to conventional transformations for the creation of new C–C bonds.[1] The enantioselective variants hold great potential in synthetic application,[2] but continue to present formidable challenges. These reactions may be limited by the absence of binding sites in hydrocarbon compounds that enable the formation of a stereochemically defined transition state for achieving high enantioselectivity. Furthermore, there are few examples of appropriate chiral ligands that tolerate the highly oxidizing conditions that are commonly used for C–H activation. In particular, the sp^3 C–H-activation-based asymmetric C–C bond-forming reaction has largely relied on metal carbenoid insertion,[3] although recent efforts have been directed toward enantioselective cross-coupling reactions involving sp^3 C–H activation.[4]



Scheme 1. General concept for the creation of sp^3 C–H bond-activation-based enantioselective oxidative coupling.

1,3-Dicarbonyl compounds of type **1** are able to coordinate to a variety of chiral Lewis acids to form chiral nucleophiles (**I**) that have been employed in various transformations with high levels of stereoselectivity.[5] Inspired by these successes, we envisioned the control of the stereochemistry in the C–H-activation-based oxidative coupling reactions (cross-dehydrogenative coupling)[6] of dicarbonyls with arylmethyl compounds (**2**) by means of a similar chiral nucleophile to induce the stereochemistry (Scheme 1).

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been used in efficient oxidative coupling reactions involving sp^3 C–H activation.[6] Sodeoka and co-workers reported the asymmetric oxidative coupling reaction of *N*-Boc-protected tetrahydroisoquinoline with malonate by using a chiral palladium catalyst and DDQ as the oxidant, which provided the desired compound in 86% *ee*.[7] Very recently, an organocatalytic asymmetric oxidative coupling of benzylic compounds with aldehydes was established with up to 86% *ee*.[8] However, to the best of our knowledge, no highly enantioselective analogues of the oxidative coupling of 3-indolylmethyl C–H bonds with malonates are available. Indole derivatives have widespread applications in organic synthesis;[9] therefore, the titled reaction holds great importance in organic synthesis. Herein, we report the highly enantioselective oxidative coupling of 3-indolylmethyl C–H bonds with malonates by sp^3 C–H-activation using a chiral Lewis acid bonded nucleophile to control stereochemistry.

We initially focused on the DDQ-oxidized coupling reaction of dimethyl malonate (**1a**) with 3-benzylindole (**2a**) in the presence of 10 mol% of $Cu(OTf)_2$ and 12 mol% of a chiral bis(oxazoline) ligand **4a**.[10] The reaction gave good enantioselectivity but a very low yield (Table 1, entry 1). The replacement of **4a** with **4b** provided a clean reaction to afford the desired product **3a** in 80% yield, albeit with 31% *ee* (Table 1, entry 2). The stereoselectivity was further enhanced by using **5a** as the ligand (64% *ee*; Table 1, entry 3). However, the substitution of metal triflates other than copper led to less-satisfactory reactions (Table 1, entries 4 and 5). Dibenzyl malonate showed comparably higher enantioselectivity than other counterparts (Table 1, entries 3, 6–7). However, **5b** and **5c** gave even lower levels of stereoselectivity than **5a** under

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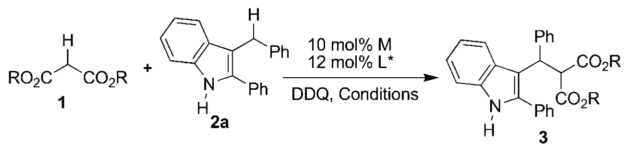
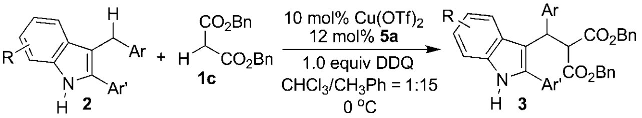
Table 1: Seeking optimal chiral Lewis acids and optimization of reaction conditions.[a]

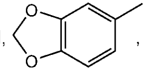


Entry	R(**1**)	Metal	L*	Solvent	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1	Me(**1a**)	$Cu(OTf)_2$	**4a**	CH_2Cl_2	18	**3a**	6	85
2	Me(**1a**)	$Cu(OTf)_2$	**4b**	CH_2Cl_2	5	**3a**	80	31
3	Me(**1a**)	$Cu(OTf)_2$	**5a**	CH_2Cl_2	6	**3a**	84	64
4	Me(**1a**)	$Mg(OTf)_2$	**5a**	CH_2Cl_2	17	**3a**	34	44
5	Me(**1a**)	$Zn(OTf)_2$	**5a**	CH_2Cl_2	22	**3a**	56	60
6	Et (**1b**)	$Cu(OTf)_2$	**5a**	CH_2Cl_2	15	**3b**	81	63
7	Bn(**1c**)	$Cu(OTf)_2$	**5a**	CH_2Cl_2	16	**3c**	90	75
8	Bn(**1c**)	$Cu(OTf)_2$	**5b**	CH_2Cl_2	5	**3c**	90	59
9	Bn(**1c**)	$Cu(OTf)_2$	**5c**	CH_2Cl_2	5	**3c**	86	53
10	Bn(**1c**)	$Cu(OTf)_2$	**5a**	CH_2Cl_2	13	**3c**	95	80[d]
11	Bn(**1c**)	$Cu(OTf)_2$	**5a**	$CHCl_3$	15	**3c**	73	90[d]
12	Bn(**1c**)	$Cu(OTf)_2$	**5a**	$PhCH_3$	16	**3c**	41	94[d]
13	Bn(**1c**)	$Cu(OTf)_2$	**5a**	–[e]	21	**3c**	99	94[d]

[a] The reaction of **1** (0.1 mmol) with **2a** (0.1 mmol) was conducted at 25 °C. [b] Yield of isolated product. [c] Determined by HPLC. [d] At 0 °C. [e] Using $CHCl_3/PhCH_3 = 1{:}15$ as solvent.

Table 2: Investigating the scope of the procedure.[a]



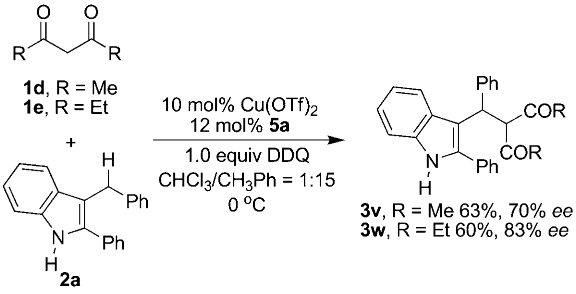
Entry	R, Ar, Ar′ (**3**)	Yield [%][b]	*ee* [%][c]
1	H, 4-BrC_6H_4, Ph (**3d**)	97	93
2	H, 4-ClC_6H_4, Ph (**3e**)	82	91
3	H, 4-FC_6H_4, Ph (**3f**)	99	90[d]
4	H, 4-MeOC_6H_4, Ph (**3g**)	74	86
5	H, 4-MeC_6H_4, Ph (**3h**)	97	91
6	H, $4\text{-NO}_2C_6H_4$, Ph (**3i**)	98	90[e]
7	H,4-CNC_6H_4,Ph(**3j**)	81	90[e,f]
8	H, 3-BrC_6H_4, Ph (**3k**)	72	93
9	H, 3-MeC_6H_4, Ph (**3l**)	96	94
10	H, 3-MeOC_6H_4, Ph (**3m**)	97	94
11	H,  , Ph(**3n**)	84	90
12	H, Ph, 4-FC_6H_4 (**3o**)	99	93
13	H, Ph, 4-ClC_6H_4 (**3p**)	99	92
14	H, 4-BrC_6H_4, 4-FC_6H_4 (**3q**)	92	94
15	H, 4-BrC_6H_4, 4-ClC_6H_4 (**3r**)	88	92
16	H, Ph, 4-MeC_6H_4 (**3s**)	70	94
17	5-Cl, Ph, Ph (**3t**)	88	95
18	5-Cl, 4-BrC_6H_4, Ph (**3u**)	78	96

[a] Unless indicated otherwise, the reaction was performed on a 0.1 mmol scale. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information). [d] At −10 °C. [e] The reaction was performed on a 0.2 mmol scale. [f] At −5 °C.

these conditions (Table 1, entries 8 and 9). Optimization of reaction parameters, including solvent and reaction temperature, revealed that halogenated solvents provided higher yields than toluene, whereas the use of nonpolar solvent and conducting the reaction at 0 °C gave higher levels of stereoselectivity (Table 1, entries 10–12). The best outcomes of conversion and enantioselectivity were achieved when the reaction was performed at 0 °C in a chloroform/toluene solvent mixture (1:15; Table 1, entry 13).

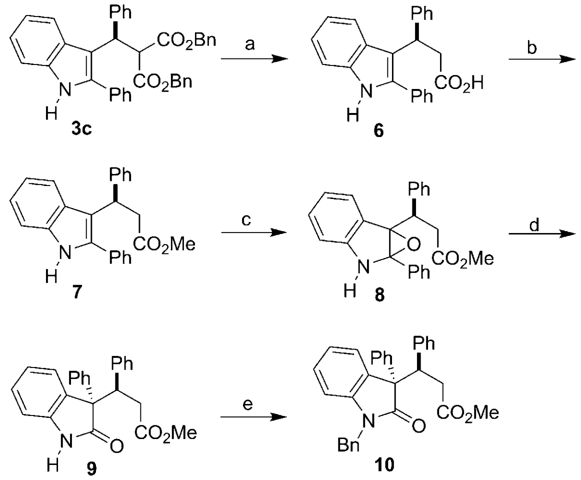
A variety of structurally diverse 3-arylmethylindole derivatives were able to participate in the asymmetric oxidative cross-coupling reaction (Table 2). This procedure was effective and highly enantioselective for either electronically rich or poor 3-arylmethyl substituted substrates (up to 99 % yield and 94 % *ee*; Table 2, entries 1–11). The electronic properties of the aryl substituent imposed no apparent influences on the stereoselectivity (86–94 % *ee*), but had a great effect on the reaction conversion. Notably, variation of the 2-aryl substituent still provided a good reaction and excellent enantiomeric purity (Table 2, entries 12–16). The introduction of substituents onto the indole moiety was well-tolerated and resulted in excellent levels of enantioselectivity (95 % and 96 % *ee*, respectively; Table 2, entries 17 and 18). The configuration of **3t** was assigned as *R* by X-ray analysis (see the Supporting Information).

Besides malonates, 1,3-diketones were also tolerated under the reaction conditions. For example, acetyl acetone (**1d**) and propionyl butanone (**1e**) both underwent oxidative coupling reactions with **2a** in good yields and high enantioselectivity [70 % and 83 % *ee*, respectively; Eq. (1)]. However, benzylic compounds, other than 3-indolylmethyl, failed to undergo the reaction. Despite this setback, the synthetic importance of indole derivatives gives this reaction great potential in asymmetric organic synthesis.



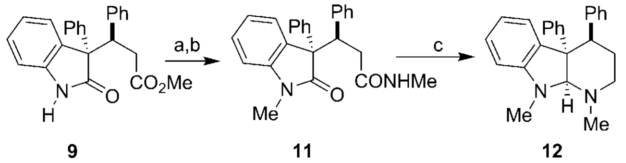
(1)

Oxindoles bearing a quaternary stereogenic center at the 3-position have great importance as building blocks in the synthesis of alkaloids.[11] The products obtained from this asymmetric cross-dehydrogenative coupling can be readily transformed into oxindoles (Scheme 2). Removal of the benzyl group on **3c** (94 % *ee*) by hydrogenation on Pd/C and followed by decarboxylation with copper(I) oxide produced **6** in 74 % yield.[12] Methylation of **6** furnished **7** in 79 % yield. Following a known procedure,[13] compound **7** was converted into oxindole **9**,[14] which contained an all-carbon quaternary stereogenic center, in 72 % overall yield whilst retaining the 94 % *ee*. The configuration of **9** was determined by X-ray analysis after it was transformed into *N*-benzylic derivative **10**. Notably, Michael addition of 3-aryl oxindoles to cinnamates to giving highly enantioenriched oxindole **9** has not been reported.



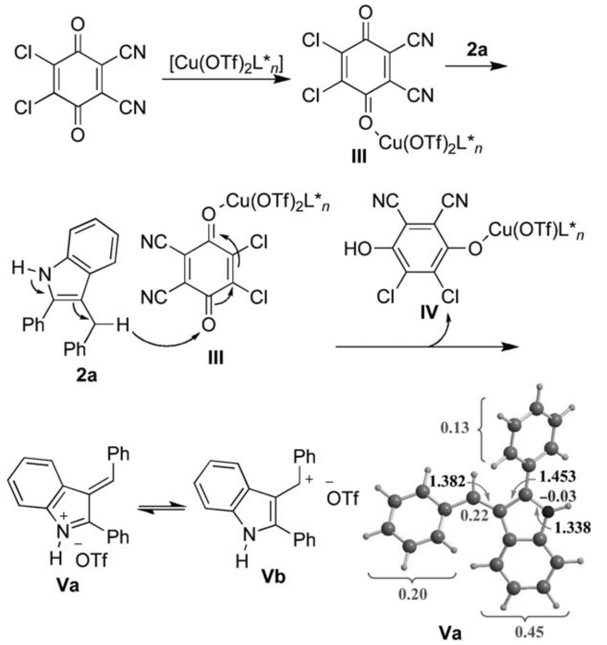
Scheme 2. Synthetic utility of the procedure and determination of stereochemistry. Reagents and conditions: a) Pd/C, H_2, MeOH, 25 °C, then Cu_2O, CH_3CN, 65 °C, 74% yield. b) $SOCl_2$, CH_3OH, 0–25 °C, 79%, 94% *ee*. c) Oxone, $NaHCO_3$, acetone/H_2O, 0 °C, 92%. d) $Sc(OTf)_3$, toluene, 110 °C, 81%, 94% *ee*. e) KO*t*Bu, BnBr, THF, 23 °C, 75%. THF = tetrahydrofuran.

2,3,4,4a,9,9a-Hexahydro-1*H*-pyrido[2,3-*b*]indoles have found widespread appearance in natural products.[15] This skeleton can be enantioselectively accessed using the reaction reported here. For example, the N-methylation of **9** with iodomethane in the presence of sodium hydride, followed by an amidation with methylamine readily produced **11**. The reductive cyclization of **11** with lithuium aluminum hydride furnished **12** in 75% yield (Scheme 3).



Scheme 3. Synthesis of 2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indole. Reagents and conditions: a) NaH, THF, MeI, RT, 81% yield. b) $MeNH_2$ (30% in MeOH), MeOH, RT, 78% yield. c) $LiAlH_4$, THF, 0 °C to RT, 75% yield.

To identify the reaction intermediate, we performed ESR studies while monitoring the reaction. The solution of DDQ in toluene exhibited a weak ESR signal whereas the addition of 3-benzylic indole, dibenzyl malonate, and the copper complex to the solution of DDQ did not show any ESR signal (see the Supporting Information, Figures S1 and S2), thus indicating that a cationic rather than radical species was generated to serve as the key intermediate of the coupling reaction.[16–18] The presence of a Lewis acid actually enhances the oxidizing ability,[19] therefore the chiral copper complex enhances the oxidizing ability by coordinating to the oxygen of DDQ to facilitate the dehydrogenation of 3-arylmethylindole (Scheme 4). Principally, the resultant cation exists as either a vinylogous iminium cation (**Va**) or a carbon cation (**Vb**). We then used DFT calculations to address the possible intermediate that participates in the reaction, which indicated that the positive charge delocalizes and distributes over the conjugate system, and thus the vinylogous iminium cation is more likely to be involved in the reaction.



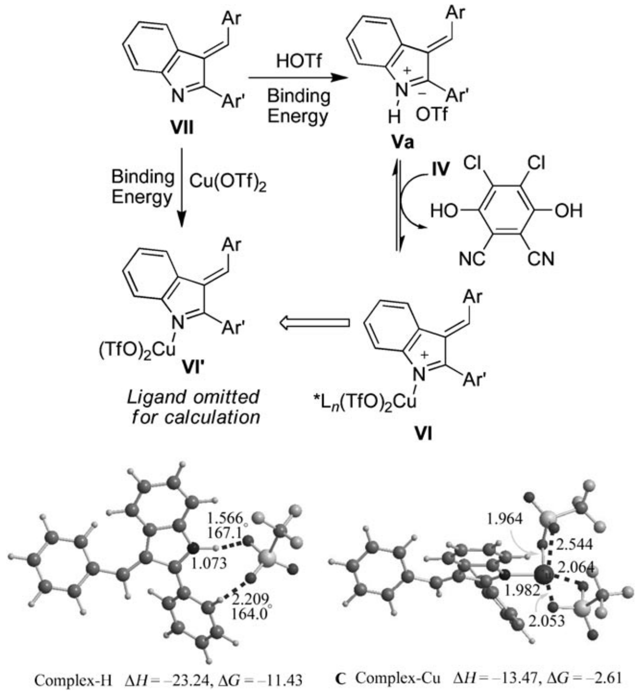
Scheme 4. Plausible pathway to generate the cation intermediate, and DFT calculation of its electron distribution.

Presumably, the vinylogous iminium cation would undergo depronation with **IV** to form a copper complex **VI**, which might be attacked by dicarbonyl compounds to give the final chiral product. However, the DFT calculation of binding energies of **VII** with HOTf and of that with $Cu(OTf)_2$ (**Va** versus **VI′**) revealed that the vinylogous iminium cation **Va** is easier to form (Scheme 5), and thus **Va** rather than **VI** is a possible reaction intermediate.

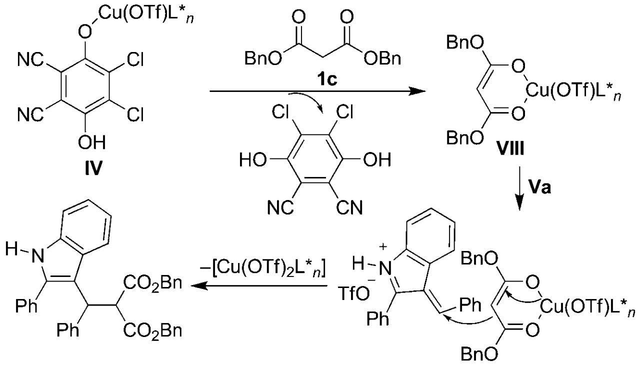
On the basis of the experimental and theoretical studies, the reaction pathway to generate chiral products has been proposed (Scheme 6). After the copper-catalyzed dehydrogenation of 3-arylmethylindole to give **Va**, the resultant copper phenoxide (**IV**) serves as a base to deprotonate the dibenzyl malonate, generating a chiral anion intermediate **VIII**, which enantioselectively attacks the vinylogous iminium cation **Va** generated from the dehydrogenation to undergo a conjugate addition, giving the chiral product. Although chiral-copper-complex-catalyzed Michael addition reactions are well-established,[5,10,20] the analogous procedure involving vinylogous iminium cations has not yet been reported.

The observed stereochemistry can be best explained by the proposed reaction models shown in Figure 1. Because of the steric repulsion between the Ar group and phenyl ring of the chiral catalyst, the transition state **IXa** is more favorably formed than **IXb** to preferentially give the desired product with observed stereochemistry (Figure 1).

In conclusion, we have reported the highly enantioselective C−H-activation-based oxidative coupling reaction of 3-arylmethylindoles with dibenzyl malonate using chiral Lewis acid catalysts. Presumably, the reaction proceeded by



Scheme 5. The DFT calculation of binding energies of **VII** with HOTf and $Cu(OTf)_2$, respectively.



Scheme 6. The reaction pathway for the generation of the product.

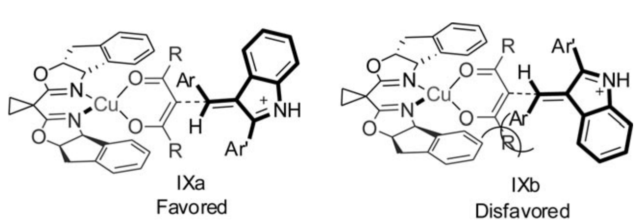


Figure 1. Plausible reaction models for the conjugate addition.

a conjugate addition of the chiral Lewis acid bonded malonate ester to the vinylogous iminium cation, formed from dehydrogenation of 3-arylmethylindoles with DDQ. This reaction thus represents an unprecedented example in which a chiral Lewis acid successfully controlled the stereochemistry of a conjugate addition reaction of a nucleophile to the vinylogous iminium cations. In addition, the protocol also represents a unique sp^3 C–H-activation-based approach to access oxindole derivatives bearing quaternary stereogenic centers with high optical purity.

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