C–H Functionalization

DOI: 10.1002/anie.201309967

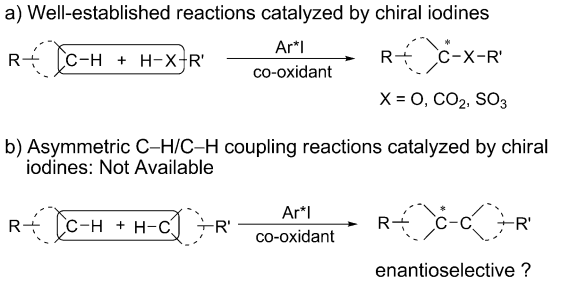
Asymmetric Organocatalytic Direct C(sp^2)–H/C(sp^3)–H Oxidative Cross-Coupling by Chiral Iodine Reagents**

*Hua Wu, Yu-Ping He, Lue Xu, Dong-Yang Zhang, and Liu-Zhu Gong**

Abstract: *An asymmetric organocatalytic direct C–H/C–H oxidative coupling reaction of N^1,N^3-diphenylmalonamides has been well established by using chiral organoiodine compounds as catalysts, wherein four C–H bonds were stereoselectively functionalized to give structurally diverse spirooxindoles with high levels of enantioselectivity. More importantly, the findings indicated that chiral hypervalent organoiodine reagents can serve as alternative catalysts for the creation of enantioselective functionalization of inactive C–H bonds.*

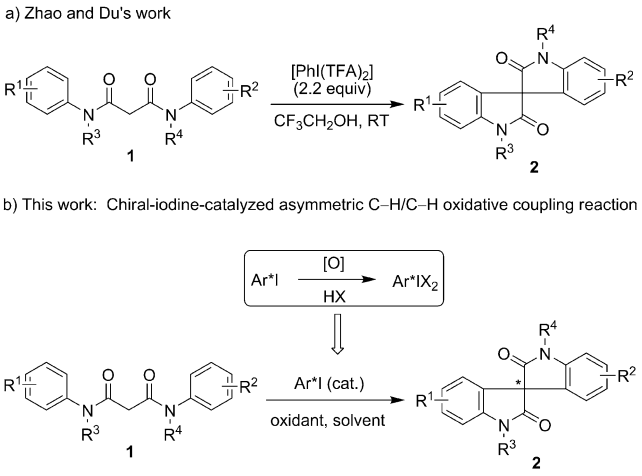
The direct oxidative cross-coupling reaction of two individual C–H bonds has been recognized as an ultimately ideal goal for the formation of carbon–carbon bonds.[1] Over the past few years the transition-metal-catalyzed oxidative cross-coupling reactions between two C–H bonds have received a great deal of attention and led to the explosive emergence of new protocols.[2] However, the field has still met with many formidable issues which continue to challenge the chemistry community. In particular, asymmetric catalytic C–H bond-coupling reactions represent the most formidable challenge. So far, there are only a limited number of successful reports describing the use of a chiral transition-metal complex to afford asymmetric coupling reactions between two C–H bonds.[3] Although asymmetric organocatalysis has achieved significant advances in the last decade, asymmetric organocatalytic asymmetric oxidative coupling reactions of C–H bonds has met with even much less success.[4] Herein, we report a direct asymmetric organocatalytic oxidative cross-coupling reaction to functionalize four C–H bonds by using chiral iodide compounds.

In recent decades, hypervalent-iodine-catalysis has enabled a variety of transformations.[5] However, enantioselective oxidative coupling reactions catalyzed by chiral hypervalent iodine remain to be developed. Thus far, there are only a few elegent examples describing chiral-organoiodine-catalyzed oxidative coupling reactions with *m*CPBA or H_2O_2 as oxidants.[6] Moreover, all these asymmetric oxidative coupling reactions, promoted by chiral organoiodine reagents, occured between C–H and C–X bonds (Scheme 1a).[6,7] In sharp contrast, enantioselective C–H/C–H oxidative coupling reactions, catalyzed by chiral hypervalent iodine (Scheme 1b), have been described to a lesser extent.



Scheme 1. Oxidative cross-coupling reaction catalyzed by an organocatalyst.

Recently, Du, Zhao, and co-workers found that the use of 2.2 equivalents of PIFA [$PhI(TFA)_2$] oxidized the anilide derivatives **1** into racemic spirooxindoles (**2**) (Scheme 2a).[8] Previous studies have revealed that aryl iodides are able to undergo oxidation reactions in the presence of oxidants to generate hypervalent iodine compounds, which actually participated in the oxidation reaction (Scheme 2b). As such, the asymmetric catalytic oxidative coupling reaction for the transformation of **1** into optically active **2** would be principally accessed by using chiral iodine reagents as organocatalysts in the presence of oxidants (Scheme 2b).



Scheme 2. Asymmetric catalytic intramolecular C–H/C–H oxidative cross-coupling reaction. TFA = trifluoroacetate.

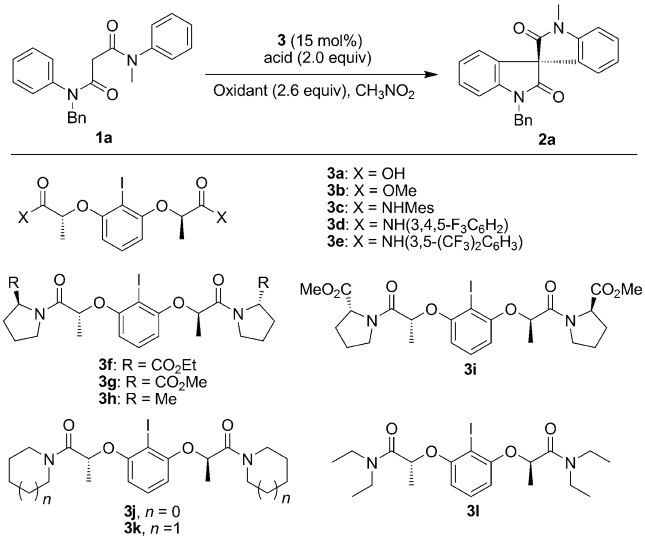
[*] H. Wu, Y. P. He, L. Xu, D. Y. Zhang, Prof. L. Z. Gong
Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026 (China)
E-mail: gonglz@ustc.edu.cn

[**] We are grateful for financial support from NSFC (21232007, 21072181), MOST (973 project 2010CB833300), and the Ministry of Education. We thank Shi-Ming Zhou for the determination of absolute configuration.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201309967.

To validate the proposed strategy (Scheme 2b), the initial investigation was performed on an asymmetric catalytic intramolecular C–H/C–H oxidative cross-coupling reaction of N^1-benzyl-N^3-methyl-N^1,N^3-diphenylmalonamide (**1a**) in the presence of 15 mol% of the chiral organoiodine **3a** and 2.6 equivalents of *m*CPBA in CH_3NO_2 at room temperature (Table 1). The transformation indeed proceeded, but furnished the desired 1-benzyl-1′-methyl-3,3′-spirobi(indoline)-2,2′-dione (**2a**) in only 23% yield and with a poor enantioselectivity (entry 1). Previous observations have suggested that the addition of either Brønsted or Lewis acids enhanced the catalytic activity of hypervalent organoiodines.[7e,9] Thus, various strong Brønsted acids and Lewis acids were evaluated to identify the best additive (entries 2–5). Among them, CF_3COOH turned out to be the preeminent acid and was able to provide **2a** with 45% yield and 31% *ee* (entry 2). With these relatively encouraging results in hand, a series of chiral iodoarenes was next examined for the enantioselective oxidative intramolecular coupling reaction of **1a** (entries 6–16). Although chiral organoiodines (**3a-e**) have successfully been applied to various protocols, as described previously,[6d,7] they showed poor enantioselectivity (entries 1 and 6–9). Inspired by conformationally-flexible design introduced by Ishihara and co-workers,[6d] modification of the chiral organoiodines by introduction of an additional stereogenic center to the original organoiodines was carried out to improve the catalytic performance, thus leading to a new family of chiral organoiodine catalysts (**3f–i**). Indeed, the organoiodines **3f–h**, synthesized from **3a** and (*S*)-proline derivatives, exhibited much higher enantioselectivity (entries 10–12). In particular, both **3f** and **3g** were able to deliever high enantioselectivities of 81 and 83% *ee*, respectively (entries 10 and 11). The comparison of the chiral iodine **3i**, which was incorporated with (*R*)-proline ester, with **3g** suggested that the (*S*)-proline ester was seemingly a matched chiral auxiliary and turned out to be slightly benificial to the stereochemical control (entry 11 versus 13). Interestingly, the installation of achiral pyrrolidine and piperidine in the catalyst, as shown in **3j**[6d] and **3k**, also gave signigficantly higher enantioselectivities (79 and 77% *ee*, respectively; entries 14 and 15) than the structually similar amides **3c–e** (up to 33% *ee*, entries 7–9). More interestingly, when the acyclic tertiary amide **3l** was employed for the reaction, high enantioselectivity (80%) was also obtained (entry 16). These results demonstrated that the tertiary amide (**3f–l**), rather than secondary amide (**3c–e**) or carboxylic acid (**3a**), played key role in inducing the high enantioselectivity. Additionally, the stereochemistry of the product was controlled by the stereogenic center close to the iodide, whereas the introduction of romote chirality exerts minor impact on the stereochemical control. Additional optimization of the reaction conditions was fouced on the oxidants. A variety of commonly used oxidants were examined and it was found that neither H_2O_2 nor TBHP was a good oxidant (entries 17 and 18).[10] Notably, the enantioselectivity could be enhanced to 86% *ee* and a good yield was also obtained by conducting the reaction using ethaneperoxoic acid ($MeCO_3H$) as the oxidant (entry 19).[11] However, the use of excess amounts of trifluoroacetic acid (4.0 equivalents) led to a slightly diminished enantiomeric excess (entry 20).

Table 1: Optimization of the transformation catalyzed by chiral organoiodine compounds.[a]

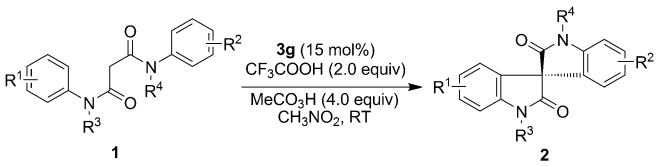


Entry	3	Oxidant	Acid	Yield [%][b]	*ee* [%][c]
1	**3a**	*m*CPBA	free	23	7
2	**3a**	*m*CPBA	CF_3CO_2H	45	31
3	**3a**	*m*CPBA	*p*-TSA	52	13
4	**3a**	*m*CPBA	TMSOTf	12	0
5	**3a**	*m*CPBA	$BF_3{\cdot}Et_2O$	–	–[d]
6	**3b**	*m*CPBA	CF_3CO_2H	44	22
7	**3c**	*m*CPBA	CF_3CO_2H	53	33
8	**3d**	*m*CPBA	CF_3CO_2H	38	7
9	**3e**	*m*CPBA	CF_3CO_2H	47	5
10	**3f**	*m*CPBA	CF_3CO_2H	52	81
11	**3g**	*m*CPBA	CF_3CO_2H	58	83
12	**3h**	*m*CPBA	CF_3CO_2H	57	71
13	**3i**	*m*CPBA	CF_3CO_2H	45	78
14	**3j**	*m*CPBA	CF_3CO_2H	47	79
15	**3k**	*m*CPBA	CF_3CO_2H	34	77
16	**3l**	*m*CPBA	CF_3CO_2H	36	80
17	**3g**	H_2O_2	CF_3CO_2H	–	–[d]
18	**3g**	TBHP	CF_3CO_2H	–	–[d]
19	**3g**	$MeCO_3H$	CF_3CO_2H	62	86[e]
20	**3g**	$MeCO_3H$	CF_3CO_2H	61	82[f]

[a] Unless indicated otherwise, the reaction of **1a** (0.1 mmol) was carried out in CH_3NO_2 (1.0 mL) at room temperature for 16 h in the presence of the chiral catalyst **3** (15 mol%), a co-oxidant (2.6 equiv), and an acid (2.0 equiv). [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis. [d] No desired product was obtained. [e] Used $MeCO_3H$ (4.0 equiv). [f] Used 4.0 equiv of CF_3CO_2H. *m*CPBA = *meta*-chloroperbenzoic acid, *p*-TSA = *para*-toluenesulfonic acid, TBHP = *tert*-butylhydroperoxide, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

To explore the generality and the substrate scope of this direct C–H/C–H oxidative coupling procedure, a range of N^1,N^3-diphenylmalonamides (**1**) was oxidized with $MeCO_3H$ (4.0 equiv) in the presence of 15 mol% **3g** under the optimized reaction conditions (Table 2). The N^1,N^3-diphenylmalonamides **1b–f**, having different substituents at both nitrogen atoms, underwent the asymmetric oxidative coupling reaction to give the corresponding spirooxindoles **2b–f** in moderate to good yields with high levels of enantioselectivity

Table 2: Scope of the intramolecular oxidative coupling reaction.[a]



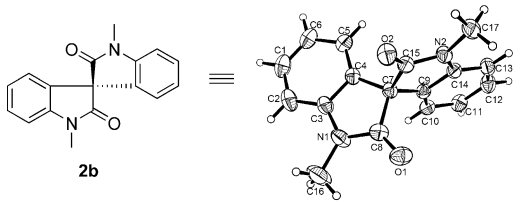
1 2

Entry	2	R^1	R^2	R^3	R^4	Yield [%][b]	*ee* [%][c]
1	**2b**	H	H	Me	Me	72	85
2	**2c**	H	H	Bn	Bn	50	90
3	**2d**	H	H	Bn	Et	45	86
4	**2e**	H	H	–	–[d]	52	86
5	**2f**	H	H	–	–[e]	40	86
6	**2g**	H	5-Ph	Bn	Bn	45	88
7	**2h**	H	5-Cl	Bn	Me	57	82
8	**2i**	H	5-F	Bn	Bn	26	84
9	**2j**	H	5-CO_2Me	Bn	Me	52	81
10	**2k**	H	5-*t*Bu	Bn	Bn	53	82
11	**2l**	H	5-OMe	Bn	Me	36	26
12	**2m**	H	7-Me	Bn	Me	41	85
13	**2n**	5′-Me	5-Me	Me	Me	78	82
14	**2o**	5′-Me	5-Me	Bn	Bn	57	85[f]
15	**2p**	5′-Me	5-Ph	Me	Bn	51	81

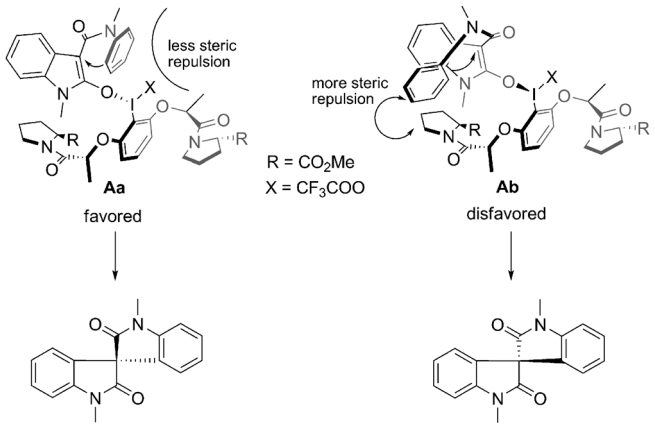
[a] Unless indicated otherwise, the reaction of **1** (0.1 mmol) was carried out in CH_3NO_2 (1.0 mL) at room temperature for 16 h in the presence of **3g** (15 mol%), $MeCO_3H$ (4.0 equiv), and CF_3CO_2H (2.0 equiv). [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis. [d] N^1,N^3-bis(2-methylbenzyl)-N^1,N^3-diphenylmalonamide was used as a substrate. [e] N^1,N^3-bis(naphthalen-1-ylmethyl)-N^1,N^3-diphenylmalonamide was used as a substrate. [f] A scale-up reaction of **1o** (1.0 mmol) was examined and afforded **2o** with 53% yield and 84% *ee*.

(up to 90% *ee*, entries 1–5). Moreover, the presence of a substituent including either a halogen, electron-withdrawing, or electron-donating group at the 4-postion of the N^1,N^3-diphenylmalonamides (**1g–k**) was well tolerated and provided the corresponding products (**2g–k**) in fairly good yields and high stereochemical outcomes (entries 6–10). However, the presence of a strong electron-donating substituent (OMe) at the 4-position of the substrate (**1l**) led to a significantly diminished enantioselectivity (entry 11). In addition, a high enantioselectivity was aslo obtained for a substrate bearing a substituent at the 2-position of the benzene ring (**1m**), albeit with a lower yield (entry 12). The disubstituted N^1,N^3-diphenylmalonamides **1n–p** also participated in the oxidative coupling reaction to furnish the corresponding **2n–p** in good yields and high optical purity (entries 13–15). The absolute configuration of **2b** was determined to be *S* by X-ray crystallographic analysis (Scheme 3).[12] The configuration of other products was assigned by analogy.

Electron-spin resonance (ESR) studies on the reaction suggested that the radical process could be excluded.[12] Alternatively, the reaction might proceed by a previously proposed pathway.[8] Actually, the intramolecular Friedel–Crafts addition of anilide to the iodo-enol intermediate **A**, as shown in Scheme 4, creates the stereogenic center. Principally, the present oxidative cyclization reaction should proceed in an SN_2' manner (*syn* addition–elimination) for associative intermediates. Because the aniline moiety of the



Scheme 3. X-ray structure of (*S*)-**2b**.



Scheme 4. The plausible intermediates to account for the stereochemistry.

intermediate **Aa** is remote from the bulky substituent the *Si* face of the 2-indololate moiety is open to nucleophilic attack by the benzene ring (*syn* addition-elimination), thus favorably giving (*S*)-**2b**. In contrast, the *Re* face of the 2-indololate moiety is shielded by the bulky cyclic amide in **Ab**, thus making the *syn* addition-elimination disfavored and leading to the generation of the enantiomer in a minor amount.

In summary, we have established the first asymmetric catalytic direct intramolecular C–H/C–H oxidative cross-coupling of N^1,N^3-diphenylmalonamides by using chiral organoiodine compound as an organocatalyst. Four C–H bonds are stereoselectively functionalized in the reaction. This transformation provides a straitforward method to access optically active spirooxindoles. More importantly, the findings imply that chiral hypervalent organoiodine reagents can serve as alternative catalysts for the creation of enantioselective functionalization of inactive C–H bonds.

Received: November 16, 2013
Revised: December 16, 2013
Published online: February 19, 2014

Keywords: asymmetric catalysis · C–H functionalization · chirality · cross-coupling · organoiodine

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[11] The low yield resulted from a side-product as described in the Supporting Information, and it was aslo reported in Ref. [8]. In addition, the opmization of conditions was unable to improve the results. For details, see the Supporting Information.

[12] The details of X-ray analytical data and ESR studies were described in the Supporting Information.

