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SHORT COMMUNICATION

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Iodide-Ion-Catalyzed Carbon–Carbon Bond-Forming Cross-Dehydrogenative Coupling for the Synthesis of Indole Derivatives

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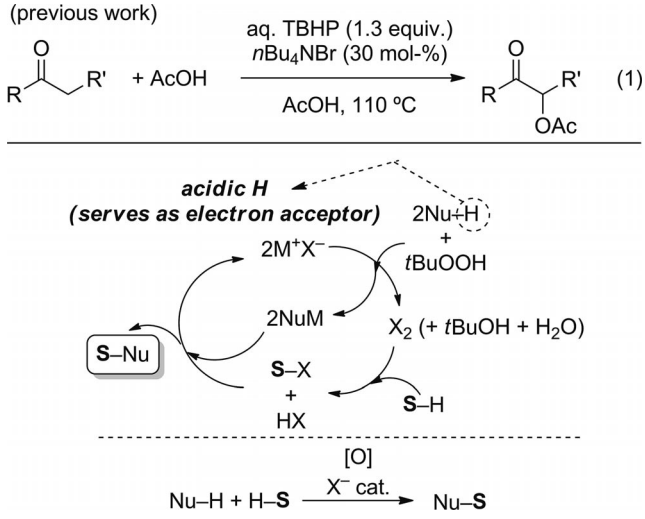
Keywords: Synthetic methods / Homogeneous catalysis / Oxidation / Cross-coupling / Nitrogen heterocycles / Iodine

The nBu$_4$NI-catalyzed intramolecular cross-dehydrogenative coupling (CDC) reaction has been applied to the synthesis of 1*H*-indole derivatives. Intramolecular oxidative coupling of *N*-arylenamines proceeded in the presence of a catalytic amount of nBu$_4$NI and *tert*-butyl hydroperoxide (TBHP) to afford the corresponding 1*H*-indole derivatives in good-to-excellent yields. A preliminary study of the synthesis of 3*H*-indole is also reported. This is a rare example of the nBu$_4$NI-catalyzed C–C bond-forming CDC reaction.

Introduction

Recently, increasing attention has been paid to the development of environmentally benign organic transformations.[1] Cross-dehydrogenative coupling (CDC) is one of the most attractive synthetic tools for such transformations.[2] Recently, we reported on a new concept of catalysis for CDC reactions by using the redox properties of halide ions; we demonstrated that the use of catalytic amounts of nBu$_4$NBr and aq. TBHP was effective for the α-acetoxylation of ketones [Scheme 1, Eq. (1)].[3] Independently, Ishihara and co-workers reported that quaternary ammonium iodide/TBHP or H_2O_2 could be used for intramolecular cycloetherification.[4] More recently, they extended the use of their catalytic system to the intermolecular α-acyloxylation of carbonyl compounds.[5] Because non-metal-catalyzed oxidative coupling reactions[6] are quite attractive, other research groups have recently focused on the use of the hydroperoxide/nBu$_4$NI system for CDC reactions (Scheme 2).[7,8] For example, Wan and co-workers reported the oxidative coupling between carboxylic acids and 1,4-dioxane under Ishihara's conditions.[9] Nachtsheim and co-workers reported the first iodide-catalyzed oxidative amination of heteroarenes,[10] and shortly afterwards Yu and



Scheme 1. Concept of our MX catalysis (**S**–H = substrate). In our previous report,[3] **S**–H = ketone and Nu–H = AcOH.

Han and co-workers reported the oxidative coupling of aminopyridines with β-keto esters.[11] Rodríguez and Moran reported the first example of a C–C bond-forming reaction by using the nBu$_4$NI/H_2O_2 system, in which a δ-alkynyl β-keto ester underwent oxidative cyclization.[12] In our previous report, we demonstrated that the oxidation of the bromide ion in MBr to bromine in the presence of an organic substance with a sufficiently acidic hydrogen (Nu–H) co-generated the corresponding conjugate base (NuM), as shown in Scheme 1. In the case of the α-acetoxylation of ketone, this NuM (AcONnBu$_4$) reacts as a nucleophile with intermediate **S**–X (α-bromo ketone) to give the product. In the course of our study on this halide-ion catalysis, we considered the use of NuM as a base instead of a nucleophile because various oxidative transformations using stoichiometric amounts of X_2 and base might be catalytic.[13] To

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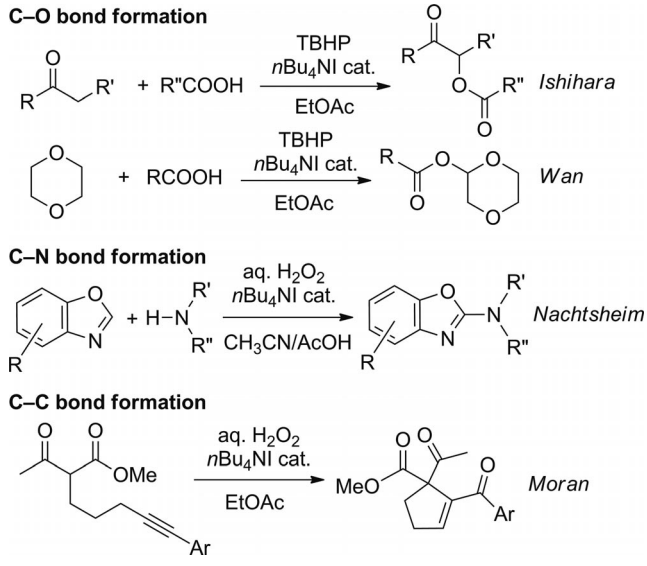
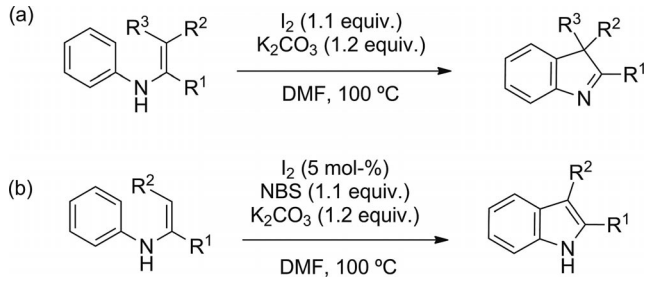
demonstrate our idea, we chose Li's indole synthesis as a model reaction. Li and co-workers recently reported the use of stoichiometric amounts of iodine and K_2CO_3 as base for the synthesis of 3*H*-indole derivatives (Scheme 3, a).[14] More recently, they extended the use of their system to the synthesis of 1*H*-indoles by using a catalytic amount of I_2 and stoichiometric amounts of *N*-bromosuccinimide (NBS) and base (Scheme 3, b).[15,16] Herein, we report on the C–C bond-forming CDC reaction using our catalyst system.



Scheme 2. Examples of nBu$_4$NI-catalyzed oxidative coupling reactions recently reported by other groups.

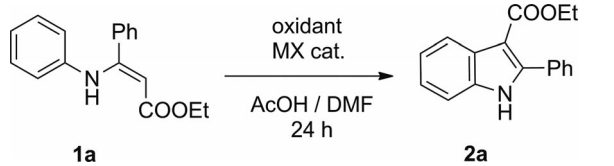


Scheme 3. (a) 3*H*-Indole synthesis and (b) indole synthesis performed with stoichiometric "X$^+$" and base, as reported by Li and co-workers.

Results and Discussion

Initially we optimized the reaction conditions for the synthesis of 1*H*-indoles by using ethyl (*Z*)-3-phenyl-3-(phenylamino)acrylate (**1a**) as a model substrate. Intramolecular oxidative coupling of **1a** with aq. TBHP as oxidant in the presence of 30 mol-% nBu$_4$NI proceeded well to afford the corresponding 1*H*-indole **2a** in 67% yield even though our previous catalytic system using nBu$_4$NBr was not effective for this transformation (Table 1, entries 1 and 2). The use of more environmentally benign aq. H_2O_2 resulted in a yield of only 39% (entry 3). The use of TBHP in decane instead of aq. TBHP gave a good yield of 83% (entry 4). Needless to say, the reaction in the absence of catalyst did not proceed at all (entry 5). A lower catalyst loading or decreased reaction temperature resulted in lower yields (entries 6 and 7). However, increasing the amount of TBHP led to an excellent yield of the indole (entry 8). Finally, the counter cation in the MI catalyst was varied and nBu$_4$N$^+$ was found to be the best (entries 8–13).

Table 1. Optimization of the reaction conditions for the CDC reaction.[a]



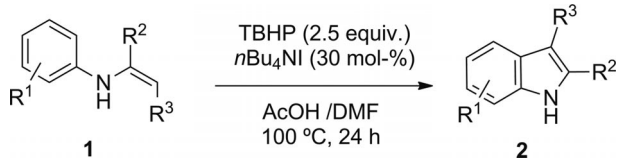
1a **2a**

Entry	Oxidant (amount [equiv.])	MX cat. (amount [mol-%])	*T* [°C]	Yield[b] [%]
1	aq. TBHP (1.5)	nBu$_4$NI (30)	100	67
2	aq. TBHP (1.5)	nBu$_4$NBr (30)	100	trace
3	aq. H_2O_2 (1.5)	nBu$_4$NI (30)	100	39
4	TBHP (1.5)[c]	nBu$_4$NI (30)	100	83
5	TBHP (1.5)[c]	none	100	0
6	TBHP (1.5)[c]	nBu$_4$NI (20)	100	44
7	TBHP (1.5)[c]	nBu$_4$NI (30)	80	49
8	TBHP (2.5)[c]	nBu$_4$NI (30)	100	91 (99)[d]
9	TBHP (2.5)[c]	LiI (30)	100	41
10	TBHP (2.5)[c]	NaI (30)	100	36
11	TBHP (2.5)[c]	KI (30)	100	57
12	TBHP (2.5)[c]	Me_4NI (30)	100	70
13	TBHP (2.5)[c]	NH_4I (30)	100	11

[a] The reactions were carried out with **1a** (0.5 mmol) in AcOH (0.25 mL)/DMF (0.25 mL). [b] Isolated yield. [c] TBHP in decane. [d] The reaction was carried out with 1.0 mmol of **1a**.

With the optimized conditions in hand, we then investigated the substrate scope of this catalytic system (Table 2). A substituent on the phenyl group at the R^2 position did not affect the efficiency of this reaction, giving the corresponding 1*H*-indoles **2b** and **2c** in yields of 97 and 93%, respectively (entries 2 and 3). A variety of electron-donating and -withdrawing groups at the R^1 position gave good-to-excellent yields (entries 4–18), although *meta*-substituted substrates such as **1f**, **1j**, and **1o** gave mixtures of regioisomers with low selectivities (entries 6, 10, and 15). Not only an ester but also a ketone functionality can be used at the R^3 position in this system (entry 19). However, a substrate with an amide moiety at the R^3 position gave a low yield, as has already been reported by Li and co-workers (entry 20).[14] The presence of alkyl groups instead of aryl groups at the R^2 position did not give reproducible results in our case because of the decomposition of the products.[17] A preliminary study of the synthesis of 3*H*-indoles was also performed (Scheme 4); the reaction of ethyl (*Z*)-2-methyl-3-phenyl-3-(phenylamino)acrylate (**3**) under the optimized conditions gave the corresponding 3*H*-indole **4** in 73% yield.

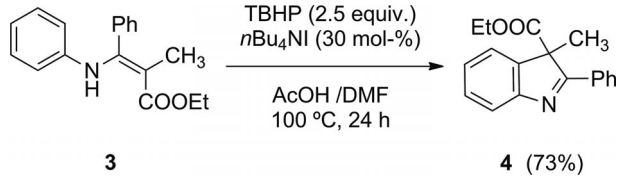
Table 2. Substrate scope of iodide-ion-catalyzed CDC reaction.



1 2

Entry	R^1	R^2	R^3	Product	Yield [%][a]
1	H	Ph	COOEt	**2a**	99
2	H	*p*BrC_6H_4	COOEt	**2b**	97
3	H	*p*$CF_3C_6H_4$	COOEt	**2c**	93
4	*p*OMe	Ph	COOEt	**2d**	84
5	*o*OMe	Ph	COOEt	**2e**	82
6	*m*OMe	Ph	COOEt	**2f/2f′**	84[b]
7	*p*OEt	Ph	COOEt	**2g**	94
8	*p*Cl	Ph	COOEt	**2h**	81
9	*o*Cl	Ph	COOEt	**2i**	81
10	*m*Cl	Ph	COOEt	**2j/2j′**	79[c]
11	*p*Br	Ph	COOEt	**2k**	95
12	*p*I	Ph	COOEt	**2l**	71
13	*p*Me	Ph	COOEt	**2m**	80
14	*o*Me	Ph	COOEt	**2n**	75
15	*m*Me	Ph	COOEt	**2o/2o′**	77[d]
16	*p*NO_2	Ph	COOEt	**2p**	78
17	*p*CF_3	Ph	COOEt	**2q**	96
18	1-naphthyl[e]	Ph	COOEt	**2r**	83
19	H	Ph	COPh	**2s**	88
20	H	Ph	CONHPh	**2t**	27

[a] Isolated yield. [b] A mixture of regioisomers was formed (**2f/2f′** = 1.1:1). [c] Combined yield of **2j** (38%) and **2j′** (41%). [d] A mixture of regioisomers was formed (**2o/2o′** = 1:2.2). [e] 1-Naphthyl was used instead of R^1-C_6H_4-.



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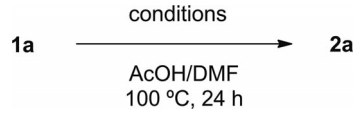
Scheme 4. Preliminary study of the synthesis of 3*H*-indole.

To confirm our hypothesis that the catalytic formation of I_2 and nBu$_4$NOAc from nBu$_4$NI and TBHP in the presence of acetic acid promoted the reaction, we carried out control experiments as shown in Table 3. Although the reaction of **1a** with 1 equiv. of I_2 in AcOH/DMF did not give the product **2a**, the addition of both 1 equiv. of I_2 and 2 equiv. of nBu$_4$NOAc promoted the reaction to afford **2a** in 85% yield (entry 2). Catalytic amounts of I_2 and nBu$_4$NOAc also promoted the reaction by using TBHP as re-oxidant (entry 3). These experiments suggest the importance of both iodine and base to the reaction. Other bases such as NaOAc, KOAc, and K_2CO_3 also promoted the reaction, but the efficiency was low, in accord with the experiments reported in Table 1 (entries 4–6). It was also confirmed that nBu$_4$NOAc does not catalyze the reaction (entry 7). Judging from these observations, we can tentatively conclude that this oxidative transformation mainly proceeds by the catalytic formation of I_2 and nBu$_4$NOAc. Because the product **2a** was obtained in 30% yield in the absence of AcOH (entry 8), we cannot completely exclude the possibility of a pathway via a hypoiodite and/or iodite formed by the direct oxidation of I^- with *t*BuOOH in the absence of a proton source.[18] The addition of TEMPO did not suppress the reaction completely, which suggests that a radical pathway does not predominate (entry 9).[19] The mechanism does not seem to be simple and further study will be needed to elucidate the detailed mechanism of this transformation.

Table 3. Control experiments.



Entry	Conditions	Yield [%][a]
1	I_2 (1 equiv.)	0
2	I_2 (1 equiv.)/nBu$_4$NOAc (2 equiv.)	85
3	TBHP[b]/I_2 (15 mol-%)/nBu$_4$NOAc (30 mol-%)	77
4	TBHP[b]/I_2 (15 mol-%)/NaOAc (30 mol-%)	50
5	TBHP[b]/I_2 (15 mol-%)/KOAc (30 mol-%)	55
6	TBHP[b]/I_2 (15 mol-%)/K_2CO_3 (30 mol-%)	44
7	TBHP[b]/nBu$_4$NOAc (30 mol-%)	0
8	no AcOH was added under the optimized conditions	30
9	TBHP[b]/nBu$_4$NI (30 mol-%)/TEMPO (1 equiv.)	41

[a] Isolated yield. [b] 2.5 equiv.

Conclusions

We have developed an iodide-ion-catalyzed intramolecular oxidative coupling of *N*-arylenamines to yield indole derivatives. This is a rare example of the nBu$_4$NI-catalyzed C–C bond-forming CDC reaction. We have demonstrated that our catalyst system, in which X_2 and MOAc are generated from the reaction of MX and hydroperoxide in the presence of AcOH, can be applied to the oxidative transformations that have been traditionally performed by using stoichiometric amounts of X_2 and base. Further applications of this halide-ion catalysis are in progress in our laboratory.

Experimental Section

General Procedure for Iodide-Ion-Catalyzed CDC Reaction: An oven-dried Schlenk flask was charged with ethyl (*Z*)-3-phenyl-3-(phenylamino)acrylate (134 mg, 0.50 mmol) and nBu$_4$NI (55 mg, 30 mol-%). The flask was sealed, evacuated, and backfilled with argon (repeated three times). AcOH (0.25 mL) and DMF (0.25 mL) were added through a syringe, and then TBHP in decane (227 mL, ca. 2.5 mmol) was added. The mixture was stirred at 100 °C for 24 h, cooled to 0 °C, and diluted with water. The mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3× 10 mL). The extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was added to a short column of silica gel and eluted by using hexane/AcOEt (3:2) as eluent. After evaporation, the residue was purified by chromatography on silica gel using petroleum ether/EtOAc (50:1) as eluent to give ethyl 2-phenyl-1*H*-indole-3-carboxylate (121 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.20 (d, J = 7.3 Hz, 1 H), 7.61–7.60 (m, 2 H), 7.40–7.38 (m, 3 H), 7.34–7.23 (m,

3 H), 4.26 (q, J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 144.5, 135.2, 132.0, 129.6, 129.1, 128.0, 127.6, 123.1, 122.1, 122.0, 111.0, 104.6, 59.7, 14.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}NO_2Na$ $[M + Na]^+$ 288.0995; found 288.1002.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data of the products, and copies of the ^1H and ^{13}C NMR spectra.

Acknowledgments

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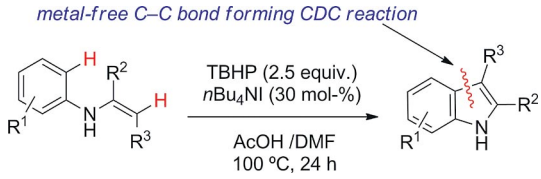
Cross-Dehydrogenative Coupling



We have found that the intramolecular oxidative coupling of *N*-arylenamines proceeds well in the presence of catalytic amounts of nBu$_4$NI (TBAI) using *tert*-butyl hydroperoxide as oxidant to afford the corresponding 1*H*-indole derivatives. This is one of the rare examples of TBAI-catalyzed C–C bond-forming CDC reactions.

Keywords: Synthetic methods / Homogeneous catalysis / Oxidation / Cross-coupling / Nitrogen heterocycles / Iodine

