C–H Activation

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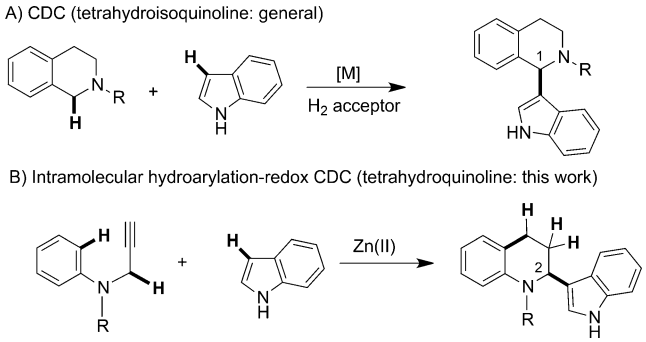
Synthesis of 2-Indolyltetrahydroquinolines by Zinc(II)-Catalyzed Intramolecular Hydroarylation-Redox Cross-Dehydrogenative Coupling of *N*-Propargylanilines with Indoles

*Guangzhe Li and Hiroyuki Nakamura**

Abstract: *An intramolecular hydroarylation-redox cross-dehydrogenative coupling (CDC) of propargylic anilines with indoles proceeded in the presence of zinc(II) catalysts to give 2-indolyltetrahydroquinolines in good to high yields. Three C–H bonds (two sp^2 and one sp^3) are activated in one shot and these hydrogen atoms are trapped by a propargylic triple bond in the molecule.*

Tetrahydroquinolines[1] and tetrahydroisoquinolines[2] are important structural motifs in pharmaceuticals and agrochemicals and hence, the development of simple yet efficient functionalization protocols is an important requirement for the discovery of biologically active compounds. The copper-catalyzed cross-dehydrogenative coupling (CDC) reaction designed by Li et al. is one of the most efficient protocols for the direct functionalization at C-1 position of tetrahydroisoquinolines (Scheme 1 A).[3,4] Although various CDC-type



Scheme 1. Indole insertion: C-1 of tetrahydroisoquinoline vs. C-2 of tetrahydroquinoline.

reactions have been reported for the synthesis of 1-indolyl tetrahydroquinolines,[5] the functionalization of tetrahydroquinolines by methods other than electrolytic transformations remains to be established.[6] Nishibayashi and co-workers succeeded in the amination at C-2 position of tetrahydroquinolines with azodicarboxylate esters mediated by visible-light photoredox catalysts, and the resulting *N*,*N*-acetals readily reacted with indoles to give 2-indolyltetrahydroquinolines.[7]

[*] Dr. G. Li, Prof. Dr. H. Nakamura
Chemical Resources Laboratory, Tokyo Institute of Technology
Yokohama, Kanagawa 226-8503 (Japan)
E-mail: hiro@res.titech.ac.jp

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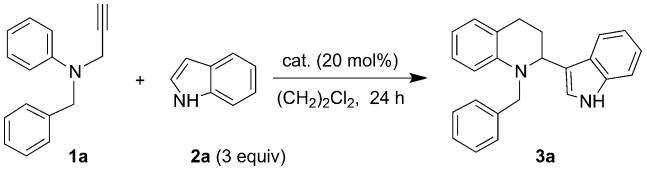
We previously reported a zinc(II)-catalyzed redox CDC reaction of propargylic amines with terminal alkynes to give *N*-tethered 1,6-enynes.[8] In this reaction, the C–C triple bond of the propargylic amine acted as a hydrogen acceptor. Here, we report a zinc(II)-catalyzed intramolecular hydroarylation-redox CDC of *N*-propargylic anilines with indoles for the synthesis of 2-indolyltetrahydroquinolines (Scheme 1 B). In the current transformation, three C–H bonds (two sp^2 and one sp^3) are activated in one shot and these hydrogen atoms are trapped by a propargylic triple bond in the molecule.

First, the hydroarylation-redox CDC of *N*-benzyl-*N*-(prop-2-ynyl)aniline (**1a**) with indole (**2a**) was examined in the presence of a catalytic amount of $ZnBr_2$ (20 mol%). It was particularly gratifying that the reaction proceeded smoothly in 1,2-dichloroethane (DCE) at 100°C as we envisaged, giving 1-benzyl-2-(1*H*-indol-3-yl)-1,2,3,4-tetrahydroquinoline (**3a**) in 60% yield along with *N*-benzyl-1,2,3,4-tetrahydroquinoline in 15% yield as the by-product (Table 1, entry 1). The reaction was also carried out in various solvents, such as toluene, 1,2-dimethoxyethane, THF, and EtOH, in the presence of $ZnBr_2$ catalyst, and aprotic non-polar solvents, such as dichloroethane, were found to promote the intramolecular hydroarylation-redox CDC (Table S1 in the Supporting Information). Next, the effects of various salts of zinc and copper were examined in dichloroethane (Table 1,

Table 1: Optimization of reaction conditions.[a]



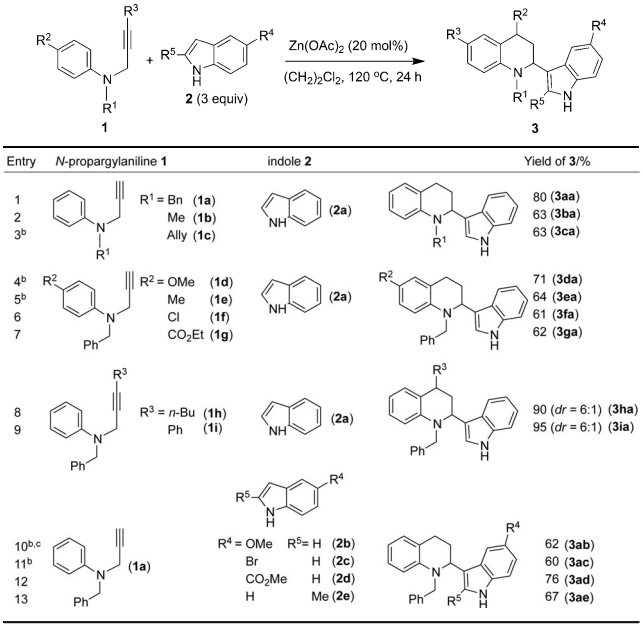
Entry	Cat.	Conc. [M]	*T* [°C]	Yield of **3a** [%][b]	Recovery of **1a** [%][b]
1	$ZnBr_2$	0.125	100	60	N.D.
2	ZnI_2	0.125	100	60	N.D.
3	$Zn(OAc)_2$	0.125	100	3	97
4	CuCl	0.125	100	7	N.D.
5	CuBr	0.125	100	20	N.D.
6	CuI	0.125	100	16	40
7	$CuCl_2$	0.125	100	20	N.D.
8	$Cu(OAc)_2$	0.125	100	31	3
9	$Zn(OAc)_2$	0.25	100	9	90
10	$Zn(OAc)_2$	0.5	100	55	45
11	$Zn(OAc)_2$	1	100	64	35
12	$Zn(OAc)_2$	1	120	82	13

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol, 3 equiv), and catalyst (0.05 mmol, 20 mol%) in dichloroethane for 24 h under nitrogen atmosphere. [b] Yields were determined by ^{1}H NMR measurement.

entries 2–8). ZnI_2 showed similar catalytic effects to $ZnBr_2$ (entry 2). When $Zn(OAc)_2$ was employed, **3a** was obtained in 3% yield with the recovery of **1a** (97% recovery; entry 3), suggesting that the generation of by-products was arrested under $Zn(OAc)_2$ catalyst conditions although the reaction rate was very low. Various copper salts were also examined, but the yields of **3a** were relatively low in all cases (entries 4–8). Interestingly, the concentration of the substrate affected the reaction yield: the yield of **3a** was increased from 9% to 64% when the concentration of **1a** was increased from 0.125 M to 1 M (entries 9–11). Further, the reaction was accelerated at 120 °C, giving **3a** in 82% yield with 13% recovery of **1a** (entry 12).

With the optimum conditions established, the intramolecular hydroarylation-redox CDC with various propargylic amines was examined next. The results are summarized in Table 2. The reaction was performed in the presence of

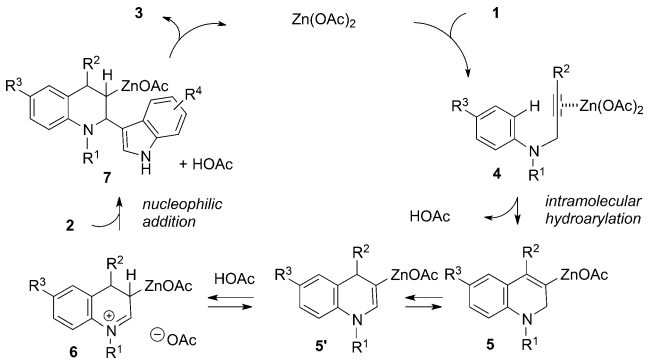
Table 2: Intramolecular hydroarylation-redox CDC of various *N*-propargylamines (**1a–i**) with indoles (**2a–e**).[a]



[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol, 3 equiv), and $Zn(OAc)_2$ (0.05 mmol, 20 mol%) in dichloroethane (0.25 mL) for 24 h under nitrogen atmosphere. [b] The reaction was carried out at 100 °C. [c] Dichloroethane (0.50 mL) was used.

$Zn(OAc)_2$ (20 mol%) in dichloroethane at 120 °C for 24 h under nitrogen atmosphere. *N*-(prop-2-ynyl)anilines ($R^2 = R^3 = H$) having various substituents at R^1, such as benzyl (**1a**) and methyl (**1b**), underwent the intramolecular hydroarylation-redox CDC with **2a** to give corresponding *N*-substituted-1,2,3,4-tetrahydroquinolines **3aa** and **3ba** in 80% and 63% yields, respectively (entries 1 and 2). The reaction took place with a C–C triple bond in the presence of a C–C double bond: *N*-allyl-1,2,3,4-tetrahydroquinoline **3ca** was predominantly obtained from **1c** in 63% yield (entry 3). Then, the effect of substituents at the *para* position (R^2 group) of an aniline moiety was examined. *N*-Benzyl-*N*-(prop-2-ynyl)anilines with various functional groups at R^2, such as methoxy (**1d**), methyl (**1e**), chloro (**1f**), and ethyl ester (**1g**) groups, also gave corresponding 6-substituted *N*-benzyl-1,2,3,4-tetrahydroquinolines **3da–3ga** in good yields, indicating that the intramolecular hydroarylation-redox CDC is applicable to substrates having labile bonds, such as Ar–Cl and ester (entries 4–7). Next, the effect of substituents at the terminal position (R^3) of propargylic anilines was investigated. Interestingly, the intramolecular hydroarylation-redox CDC of *N*-benzyl-*N*-(prop-2-ynyl)anilines having substituents at R^3, such as *n*-butyl (**1h**) and phenyl (**1i**), proceeded smoothly with **2a** and resulting cyclized products, **3ha** and **3ia**, were obtained in high yields (90% and 95%, respectively). The diastereomeric ratios of both products were approximately 6:1 as calculated from ^1H NMR data. Finally, the effect of substituents at R^4 of the indole ring was examined. Indoles with an electron-donating group, such as a methoxy (**2b**) group, or electron-withdrawing groups, such as bromo (**2c**) and methyl ester (**2d**) groups, at R^4, and 2-methylindole (**2e**) were employed in the reaction to afford corresponding *N*-benzyl-1,2,3,4-tetrahydroquinolines **3ab–3ae** in 60–76% yields (entries 10–13).

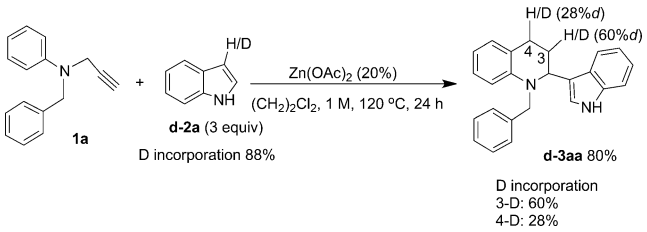
A plausible mechanism for the intramolecular hydroarylation-redox CDC is shown in Scheme 2. It was reported that *N*-phenyl-*N*-(prop-2-yn-1-yl)anilines **1** underwent intramolecular hydroarylation in the presence of various transi-



Scheme 2. Plausible mechanism for the intramolecular hydroarylation-redox CDC.

tion-metal catalysts, including platinum,[9] gold,[10] and rhodium complexes.[11] Therefore, first, *N*-substituted 1,2-dihydroquinoline **5** would be generated from zinc-activated complex **4** via intramolecular hydroarylation. Then, an equilibrium would be established among dihydroquinoline **5**, dihydroquinoline **5′**, and iminium cation **6**, and **6** would undergo nucleophilic addition reaction with indole **2** to afford the cyclized product **3** through intermediate **7**. Indeed, a deuterium labeling study that used 3-deuteroindole **d-2a** revealed that 60% and 28% of deuterium were, respectively incorporated at C3 and C4 positions of *N*-benzyl-1,2,3,4-tetrahydroquinoline **3aa** (Scheme 3), suggesting the establishment of an equilibrium among **5**, **5′**, and **6**. The nucleophilic addition of indole **2** to the intermediate **6** would be accelerated under more concentrated conditions of catalysts.

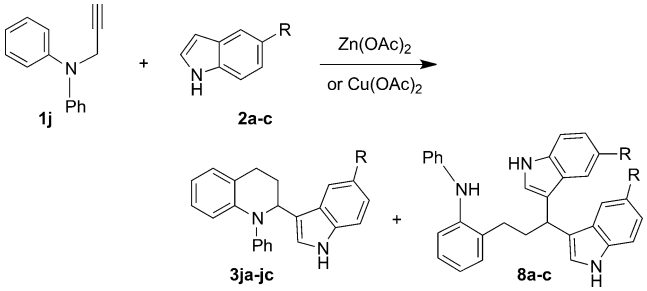
Interestingly, when *N*-phenyl-*N*-(prop-2-yn-1-yl)aniline (**1j**) was employed in the intramolecular hydroarylation-



Scheme 3. Deuterium labeling study.

redox CDC with indole (**2a**) in dichloroethane, the expected *N*-phenyl-1,2,3,4-tetrahydroquinoline **3ja** was obtained in only 24% yield along with the generation of diindole-substituted ring-opening product **8a** as the major product in 75% yield (Table 3, entry 1). The use of 4 equivalents of **2a**

Table 3: Intramolecular hydroarylation-redox CDC and diindole-substituted ring-opening reactions of *N*-phenyl-*N*-(prop-2-yn-1-yl)aniline (**1j**).[a]

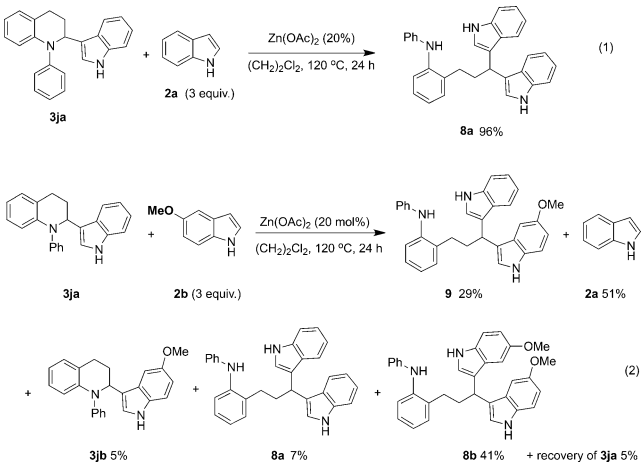


Entry	Indole	Yield of **3** [%]	Yield of **8** [%]
1[a]	**2a** (R = H)	24 (**3ja**)	75 (**8a**)
2[b]	**2a**	N.D. (**3ja**)	98 (**8a**)
3[b]	**2b** (R = OMe)	N.D. (**3jb**)	89 (**8b**)
4[c]	**2c** (R = Br)	9 (**3jc**)	72 (**8c**)
5[d]	**2a**	65 (**3ja**)	N.D. (**8a**)

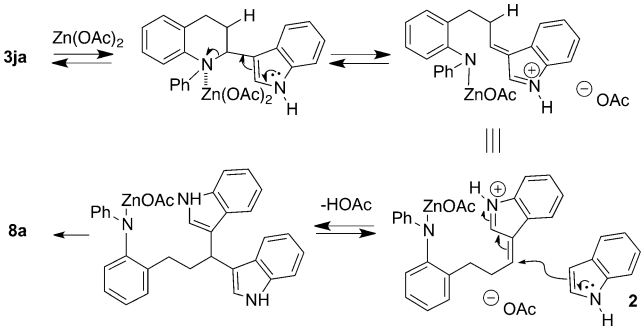
[a] Reaction conditions: **1j** (0.25 mmol), **2a** (0.75 mmol, 3 equiv), and $Zn(OAc)_2$ (20 mol%) in dichloroethane (0.25 mL) at 120°C for 24 h under nitrogen. [b] Four equivalents of **2a** (1.0 mmol) was used. [c] Four equivalents of **2a** (1.0 mmol) was employed in toluene at 150°C. [d] Reaction conditions: **1j** (0.25 mmol), **2a** (0.5 mmol, 2 equiv), and $Cu(OAc)_2$ (20 mol%) in dichloroethane (0.5 mL) at 100°C for 12 h under nitrogen.

afforded **8a** predominantly (entry 2). Whereas 4-methoxyindole (**2b**) gave disubstituted ring-opening product **8b** predominantly (89% yield) under the same conditions, 4-bromoindole (**2c**) required a higher reaction temperature for the reaction to proceed. Indeed, the corresponding disubstituted ring-opening product **8c** was obtained in 72% yield at 150°C in toluene using a sealed tube, along with a small amount of cyclized product **3jc** (9% yield, entry 4). The intramolecular hydroarylation-redox CDC proceeded predominantly when the reaction was carried out in the presence of $Cu(OAc)_2$ (20 mol%) at 100°C in dichloroethane for 12 h, revealing that both the intramolecular hydroarylation-redox CDC and the diindole-substituted ring-opening reaction can be controlled by the selection of the catalyst.

To clarify the generation mechanism of the diindole-substituted products, two reactions were examined. When *N*-phenyl-1,2,3,4-tetrahydroquinoline **3ja** was treated with 3 equivalents of indole **2a** in the presence of $Zn(OAc)_2$ (20 mol%) at 120°C in dichloroethane for 24 h, diindole-substituted ring-opening product **8a** was obtained in 96% yield [Eq. (1)]. Furthermore, when **3ja** was treated with 5-methoxy-1*H*-indole **2b** instead of **2a**, five products were obtained along with the recovery of **3ja** (5% yield), as shown in [Eq. (2)]. 2-(3-(1*H*-indol-3-yl)-3-(5-methoxy-1*H*-indol-3-yl)propyl)-*N*-phenylaniline **9** was obtained from **3ja** through a ring-opening reaction similar to Equation (1). *N*-phenyl-1,2,3,4-tetrahydroquinoline **3jb** was probably produced from **9** in which indole **2a** acted as the leaving group. Diindole-substituted ring-opening products **8a** and **8b** were generated from corresponding *N*-phenyl-1,2,3,4-tetrahydroquinolines **3ja** and **3jb**, and indoles **2a** and **2b**, respectively.



Based on these observations, the generation mechanism of diindole-substituted ring-opening product **8a** is shown in Scheme 4. The nitrogen atom of 1,2,3,4-tetrahydroquinoline **3ja** would coordinate with $Zn(OAc)_2$ to induce the ring-opening reaction, and the resulting iminium cation would undergo nucleophilic attack by indole **2a** to afford corresponding diindole-substituted ring-opening product **8a**. The reaction is probably reversible and diindole-substituted ring-opening product **8a** can be cyclized under the zinc-catalyzed conditions to give cyclized product **3ja** with the release of an indole molecule as the leaving group.



Scheme 4. Plausible mechanism for the generation of **8a**.

In conclusion, we succeeded in the synthesis of 2-indolyltetrahydroquinolines via the zinc(II)-catalyzed intramolecular hydroarylation-redox CDC of *N*-propargylic anilines with indoles. Three C–H bonds (two sp^2 and one sp^3) were activated in one shot and these hydrogen atoms were trapped by a propargylic triple bond in the molecule. As a functionalization protocol for tetrahydroquinolines has not been established yet, we believe that the intramolecular hydroarylation-redox CDC is one of the useful strategies for the functionalization at C-2 position of tetrahydroquinolines. Work aimed at further extension of the redox CDC is in progress.

Keywords: C–H activation · cross-dehydrogenative coupling · intramolecular hydroarylation · tetrahydroquinoline · zinc catalysts

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