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Graphical Abstract

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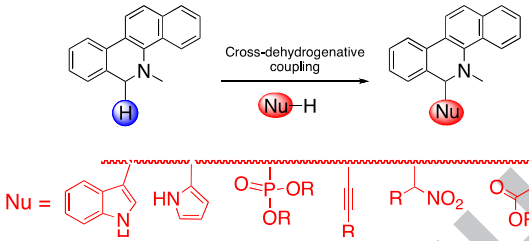

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Synthesis of *N*-methyl-5,6-dihydrobenzo[c]phenanthridine and its sp^3 C(6)–H bond functionalization via oxidative cross-dehydrogenative coupling reactions

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ABSTRACT

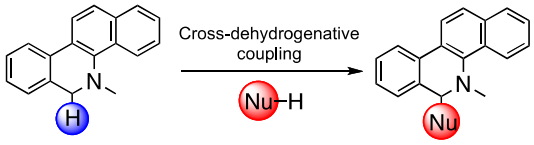
An expeditious route involving a Pd-catalyzed intramolecular biaryl-coupling for the synthesis of the *N*-methyl-5,6-dihydrobenzo[c]phenanthridine scaffold has been developed. For the first time, we herein report the sp^3 C(6)-H functionalization of this heterocyclic scaffold through DDQ-mediated cross-dehydrogenative coupling reactions with nitroalkanes, dialkyl malonates, alkynes, dialkyl phosphites, carbonyl compounds, pyrrole, and indoles.

Introduction

The *N*-methyl-5,6-dihydrobenzo[c]phenanthridine (**1**, DHB) represents a common scaffold of several bioactive alkaloids of the benzophenanthridine family.[1,2] Members of this family have drawn the attention of researchers due to their broad spectrum of pharmacological properties such as antimicrobial, antifungal, and antiproliferative activities.[1-4] Notwithstanding that several synthetic strategies have been reported for natural and non-natural compounds having the benzophenanthridine scaffold,[5-9] the direct C–H functionalization of this heterocycle remains unexplored as an alternative strategy to generate structural diverse compounds in the quest for new drugs.[10,11] As part of our continued interest in the development or application of synthetic methods to the functionalization of heterocyclic scaffolds that occur in natural products,[12] we recently became interested in the direct sp^3 C–H functionalization of DHB (**1**). Considering that the sp^3 C–H functionalization of **1** can not only occur at the position 6 but also at the methyl group, we specifically explored the sp^3 C-H activation and functionalization at position 6 through oxidative cross-dehydrogenative coupling (CDC) reactions with suitable nucleophiles.

Considerable progress has been made in the development of CDC reactions between diverse nucleophiles and nitrogen-containing heterocycles such as tetrahydroisoquinolines (THIQs) and benzylamine derivatives.[13] Copper-catalyzed CDC reactions between *N*-aryl-THIQ and indoles or activated methylenes have been developed by Li *et al.*[14,15] Niu *et al.* reported the functionalization of tertiary benzylamines using acetylides as nucleophiles.[16] Using a similar strategy, Zheng *et al.* performed the alkynylation of THIQs.[17] Zhu *et al.*[18] developed the functionalization of THIQs via oxidative multicomponent reactions using 2-iodoxybenzoic acid as oxidant, while Prabhu *et al.*[19] reported the same reaction using O_2 as the oxidant and different nucleophiles such as nitroalkanes, carbonyl compounds, coumarins, and phosphites. Recent investigations have reported the efficient application of the well-known oxidant, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in C-C bond forming reactions through benzylic C-H bond activation.[20]

Taking the previously described literature into consideration, we postulated DHB (**1**) as an attractive heterocyclic scaffold to explore the scope of the CDC reaction. Therefore, we herein report an expeditious route for the synthesis of the heterocycle **1** followed by its sp^3 C(6)-H functionalization through a Cu-catalyzed cross-dehydrogenative coupling using DDQ as oxidant and different nucleophiles (Scheme **1**).



1 **2**

Scheme 1. Representative CDC reaction between *N*-methyl-5,6-dihydrobenzo[c]phenanthridine (**1**) and nucleophiles.

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Table 1. Optimization for the preparation of *N*-methyl-5,6-dihydrobenzo[c]phenanthridine (**1**).[a]

Entry	Catalyst	Ligand	Base	Temperature (°C)	Time (h)	Isolated yields (%)
1	$PdCl_2$	PPh_3	K_2CO_3	140	24	NR
2	$PdCl_2$	PPh_3	K_2CO_3	140	24	NR[b]
3	$Pd(PPh_3)_4$	-	K_2CO_3	140	24	NR
4	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	K_2CO_3	140	24	9[c]
5	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	K_2CO_3	140	24	16[d]
6	$Pd(OAc)_2$	P(*o*-tol)$_3$	K_2CO_3	140	24	8[d]
7	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Na_2CO_3	140	24	NR
8	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	K_3PO_4	140	24	NR
9	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	AcONa	140	24	NR
10	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	*t*-BuOk	140	12	18
11	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	*t*-BuOk	130	12	25
12	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	t-BuOk	110	12	36[d,e]
13	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	140	24	42
14	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	140	24	45[d]
15	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	130	12	40
16	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	130	6	79[d,f]

[a]Reaction conditions: Compound **6** (1 equiv), catalyst (20 mol%), ligand (40 mol%), base (2 equiv), DMA (0.2 M).

[b]Reaction carried out in dimethylformamide.

[c]Catalyst (10 mol%).

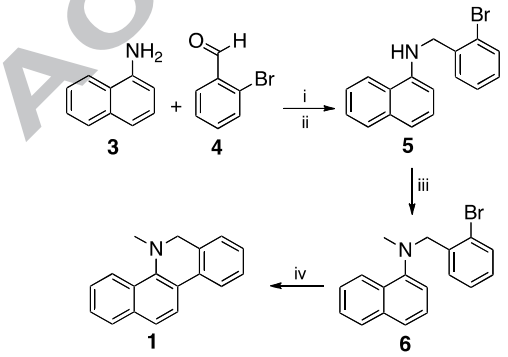
[d]Base (2.5 equiv).

[e]Reaction carried out in toluene.

[f]Catalyst (30 mol%) and ligand (60 mol%).

Results and Discussion

At the outset of our work, the DHB (**1**) was chosen as an interesting scaffold to explore its sp^3 C(6)-H functionalization, so an expedient synthetic route was carried out as outlined in Scheme 2. First, the 2-bromo-*N*-(α-naphthyl)benzylamine (**5**) was synthesized in excellent yield (94%) by reductive amination between 1-naphthylamine (**3**) and 2-bromobenzaldehyde (**4**) using $NaBH_3CN$ as the reducing agent. Next, the *N*-methyl-(2-bromobenzyl)naphthylamine (**6**) was efficiently obtained by methylation of **5** with NaI and CH_3I in THF. In the final step the cyclization of **6** into **1** was achieved by a palladium-catalyzed intramolecular biaryl-coupling (Scheme **2**) and the results of the optimization experiments are summarized in Table 1.



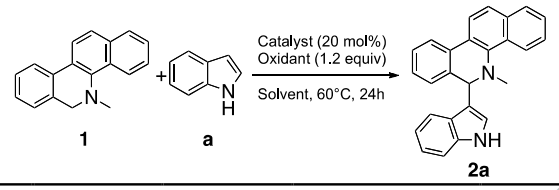
Scheme 2. Synthesis of *N*-methyl-5,6-dihydrobenzo[c]phenanthridine (**1**). Reaction Conditions: i) $InCl_3$ (5 mol%), rt, 1 h, DCM. ii) $NaBH_3CN$ (3 equiv), DCM:MeOH, 0 °C to rt, 16 h. iii) a) NaH, THF, 0 °C to rt, 30 min, CH_3I, THF, rt, 16 h. iv) DHB (1 equiv), $Pd(OAc)_2$ (30 mol%), $Cy_3P{\cdot}HBF_4$ (60 mol%), Cs_2CO_3 (2.5 equiv), DMA (0.2 M), 130 °C, 6 h.

Our initial efforts using $PdCl_2/PPh_3$ or $Pd(PPh_3)_4$ in the presence of K_2CO_3 failed to give the desired product at 140 °C in *N,N*-dimethylacetamide (DMA) or dimethylformamide (Table 1, entries 1-3).[21] However, the combination of $Pd(OAc)_2$ and $Cy_3P{\cdot}HBF_4$ in the presence of K_2CO_3 gave the desired product in low yields (entries 4-5), even when the $Cy_3P{\cdot}HBF_4$ ligand was replaced by P(*o*-tol)$_3$ (entry 6). The replacement of K_2CO_3 by other weak bases such as Na_2CO_3, K_3PO_4, and AcONa proved to be inefficient to favor the coupling process (entries 7-9), but the use of a stronger base like *t*-BuOK slightly improved the yield of **1**, resulting a more efficient reaction when the temperature was decreased to 130 °C or the solvent was replaced by toluene (entries 10-12). Interestingly, compound **1** was achieved in better yields (42% and 45%) by using 2 or 2.5 equiv of Cs_2CO_3 as the base in DMA at 140 °C (entries 13-14). When the coupling reaction was performed at 130 °C for 12 h, a slightly decrease in yield from 45% to 40% was observed (entry 15). Further experiments revealed that a shorter reaction time (6 h) was a critical factor to increase yield of product **1** from 40% to 79% (entry 16). Therefore, the optimal conditions for the intramolecular biaryl-coupling reaction of compound **6** were reached by using 1 equiv of **6**, 30 mol% of $Pd(OAc)_2$, and 60 mol% of $Cy_3P{\cdot}HBF_4$ in DMA at 130 °C for 6 h.

With the heterocyclic scaffold **1** in hand; we carried out a set of experiments to optimize the reaction conditions for the CDC between **1** and indole, which was taken as the model reaction (Table 2). Based on the reaction conditions reported by Prabhu *et*

al.,[19] the use of I_2 as catalyst in polar solvents (DCM:MeOH or MeOH) under aerobic conditions failed to provide the desired product **2a** at 60 °C (Table 2, entries 1 and 2). To circumvent this, we explored iron and ruthenium catalysts ($FeCl_2$, $FeCl_3$, or $RuCl_3$) in combination with *tert*-butyl hydroperoxide or hydrogen peroxide, but the product **2a** was obtained in low yields (entries 3-5). Considering that DDQ has been reported to be an efficient reagent that promotes CDC reactions, our next experiment was performed using this oxidant. At first we used DDQ as the sole oxidant in toluene, but the desired compound **2a** was obtained in 30% yield (entry 6). However, the combination of DDQ with 20 mol% of CuBr afforded the product in 45% yield (entry 7). To circumvent the unsatisfactory dissolution of DDQ in all previous experiments, a 1:1 mixture of CH_3CN:toluene was attempted. To our delight, the CDC between **1** and indole furnished the desired product **2a** in good yield (60%) once the solubility of DDQ and the temperature were increased (entry 8). Additional experiments were carried out to examine the use of CuBr in the absence of DDQ and to determine the minimum loading of CuBr for the desired CDC reaction. In the absence of DDQ, the copper catalyst moderately promoted the coupling between **1** and indol (entry 9). When the amount of CuBr was decreased to 10 and 3 mol%, the yields decreased dramatically (entries 10 and 11).

Table 2. Optimization for the synthesis of product **2a**.[a]

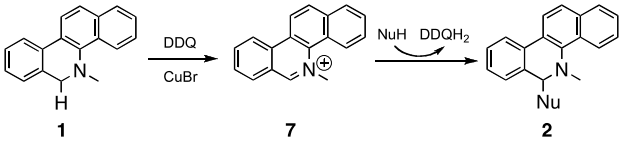


Entry	Catalyst	Oxidant	Solvent	Isolated yields (%)
1	I_2	O_2	CH_2Cl_2:CH_3OH	-
2	I_2	O_2	CH_3OH	-
3	$RuCl_3$	O_2	CH_3OH	20
4	$FeCl_3$	TBHP	$ClCH_2CH_2Cl$	13[b]
5	$FeCl_2$	H_2O_2	CH_3OH	7
6	-----	DDQ	$PhCH_3$	30
7	CuBr	DDQ	$PhCH_3$	45
8	CuBr	DDQ	CH_3CN:$PhCH_3$	60[c]
9	CuBr	-----	CH_3CN:$PhCH_3$	31
10	CuBr	DDQ	CH_3CN:$PhCH_3$	31[d]
11	CuBr	DDQ	CH_3CN:$PhCH_3$	8[e]

[a]Reaction conditions: Compound **1** (1 equiv), compound **a** (1.2 equiv), oxidant (1.2 equiv), catalyst (20 mol%), solvent (0.2 M), 60 °C, 24 h. [b]2 equiv of TBHP. [c]Reaction carried out at 80 °C. [d]Catalyst (10 mol%). [e]Catalyst (3 mol%).

To explore the scope of this methodology, we incorporated various types of nucleophiles into compound **1** (Table 3). The CDC between **1** and 2-methylindole afforded the desired product **2b** in 56% yield. However, performing the standard reaction with pyrrole resulted in lower yields of product **2c** (39%). It is worth noting that methyl and ethyl malonates underwent moderate coupling reaction with compound **1** to furnish derivatives **2d**-**2e** (40% yield), but the CDC reaction proved to be less efficient with the Meldrum's acid despite it is more acidic than the malonates (product **2f** in 22% yield). Similarly, the coupling reaction of **1** with ethyl acetoacetate and acetophenone gave desired compounds **2g** and **2h** in low yields (20% and 18%, respectively). It is worth to mention that the ^{1}H-NMR spectra of product **2g** showed a double splitting pattern for two main isomers (see supplementary material). The proton H-6 split (δ 5.0 ppm) into a doublet with a coupling constant of J = 11.4 Hz, indicating that the methine proton of the nucleophile (CH_3-CO-**CH**-CO_2-CH_2CH_3) adopts an antiperiplanar rather than a gauche conformation. Therefore, the CH_3-CO- and -CO_2-CH_2CH_3 groups are gauche to H-6 and their positions can be interchanged to explain the two main isomers in NMR. Geometry optimization of all major conformers of **2g** using molecular mechanic force fields (MMX) as implemented in the PCMODEL software, resulted in two minimum energy structures having the antiperiplanar conformations.[22] Then we turned our attention to the carbon–phosphorous coupling reaction, which produced the α-aminophosphonates **2i** and **2j** in low yields under the standard conditions. We then extended the CDC reaction to nitroalkanes, obtaining the nitro derivatives **2k**-**2m** in low and moderate yields (55%, 32%, and 25%), which suggested that the progress of the coupling reaction decreases with increasing chain length of the nitroalkanes. To our surprise, the ^{1}H-NMR spectra of the nitroethane and nitropropane derivatives (**2l** and **2m**) exhibited splitting patterns for a single isomer (see supplementary material). It should be noted that no other nitroethane and nitropropane derivatives were observed on thin layer chromatography or NMR. The proton H-6 split (δ 4.58 ppm) into a doublet with a coupling constant of J = 10.5 Hz, indicating that the methine proton of the nucleophile (CH_3-**CH**-NO_2) adopts an antiperiplanar conformation. According to the molecular modeling by PCMODEL, the minimum energy structures of **2l** are those with the CH_3- and -NO_2 groups gauche to H-6, being more stable the conformer with the -NO_2 group oriented towards the heterocyclic nitrogen (see supplementary material). A similar outcome was observed for compound **2m**, which exhibited a doublet (δ 4.60 ppm) with J = 10.5 Hz, characteristic of the antiperiplanar conformation. On the other hand, the trimethylsilyl cyanide reacted with compound **1** to give the nitrile **2n** in moderate yield. To our delight, the CDC reaction proceeded smoothly by using alkynes and the desired products **2o** and **2p** were afforded in good yields (60% and 70%, respectively). Notwithstanding the range of yields, the described oxidative CDC reaction can be extended to the synthesis of a structurally diverse chemical library starting from the heterocyclic scaffold **1**.

A preliminary mechanistic proposal for the CDC reaction is depicted in Scheme **3**. Based on previous observations about DDQ/Cu-mediated processes,[20a] the iminium ion **7** is assumed to be the reaction intermediate, which further reacts with the nucleophile to furnish the expected product (Scheme **3**).



Scheme 3. Plausible mechanism for the CDC of **1** with nucleophiles.

Conclusions

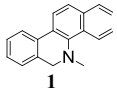
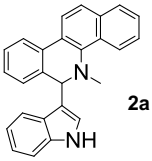
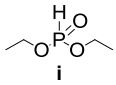
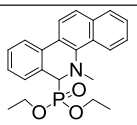
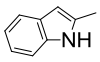
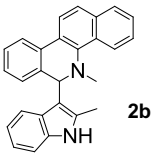
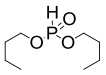
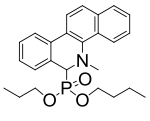
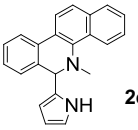
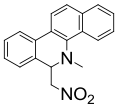
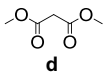
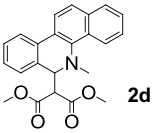
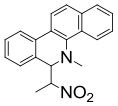
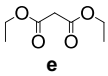
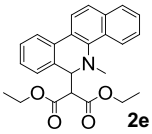
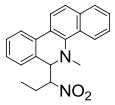
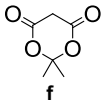
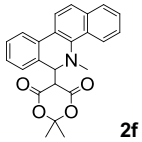
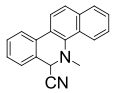
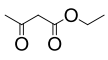
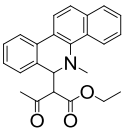
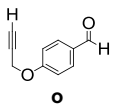
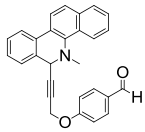
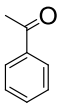
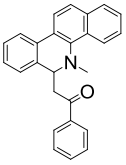
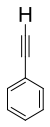
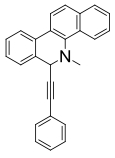
In summary, the *N*-methyl-5,6-dihydrobenzo[c]phenanthridine (**1**) was prepared in a novel and expedient three-step synthetic sequence. Moreover, the sp^3 C(6)–H bond functionalization of the heterocyclic scaffold **1** was achieved through a CuBr/DDQ-mediated cross-dehydrogenative coupling reaction, using a wide variety of nucleophiles such as nitroalkanes, dialkyl malonates, alkynes, dialkyl phosphites, carbonyl compounds, pyrrole, and indoles. It is worth mentioning that these experiments represent

the first example of sp^3 C–H bond functionalization onto the 5,6-dihydrobenzo[c]phenanthridine heterocyclic system. We are currently extending this methodology to the sp^3 C–H bond functionalization of natural products having the dihydrobenzo[c]phenanthridine scaffold.

Supplementary data

Supplementary data (experimental procedures, spectroscopic and spectrometric data for all new compounds) associated with this article can be found, in the online version, at doi:

Table 3. CDC reaction of DHB (1) with several nucleophiles.

Entry	1	2	Product	Yield [%][b]	Entry	1	2	Product	Yield [%][b]
1			 **2a**	60	**9**	1		 **2i**	30
2	1		 **2b**	56	**10**	1		 **2j**	41
3	1		 **2c**	39	**11**	1	H_3C-NO_2 **k**	 **2k**	55[d]
4	1		 **2d**	40[c]	**12**	1		 **2l**	32[d]
5	1		 **2e**	40[c]	**13**	1		 **2m**	25[d]
6	1		 **2f**	22	**14**	1		 **2n**	42
7	1		 **2g**	20	**15**	1		 **2o**	60
8	1		 **2h**	18	**16**	1		 **2p**	70

Reaction conditions: [a]Compound **1** (1 equiv), nucleophile (1.2 equiv), DDQ (1.2 equiv), CuBr (20 mol%), 50:50 v/v CH_3CN:$PhCH_3$ (0.2 M), 80°C, isolated yields in parenthesis. [b] Yields of isolated products based on DHB. [c]Cs_2CO_3 (1.2 equiv.) was added. [d]2 equiv of nucleophile were added.

Acknowledgments

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Table 1. Optimization for the preparation of *N*-methyl-5,6-dihydrobenzo[c]phenanthridine (**1**).[a]

Entry	Catalyst	Ligand	Base	Temperature (°C)	Time (h)	Isolated yields (%)
1	$PdCl_2$	PPh_3	K_2CO_3	140	24	NR
2	$PdCl_2$	PPh_3	K_2CO_3	140	24	NR[b]
3	$Pd(PPh_3)_4$	-	K_2CO_3	140	24	NR
4	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	K_2CO_3	140	24	9[c]
5	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	K_2CO_3	140	24	16[d]
6	$Pd(OAc)_2$	P(*o*-tol)$_3$	K_2CO_3	140	24	8[d]
7	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Na_2CO_3	140	24	NR
8	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	K_3PO_4	140	24	NR
9	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	AcONa	140	24	NR
10	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	*t*-BuOk	140	12	18
11	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	*t*-BuOk	130	12	25
12	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	t-BuOk	110	12	36[d,e]
13	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	140	24	42
14	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	140	24	45[d]
15	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	130	12	40
16	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	130	6	79[d,f]

[a]Reaction conditions: Compound **6** (1 equiv), catalyst (20 mol%), ligand (40 mol%), base (2 equiv), DMA (0.2 M).

[b]Reaction carried out in dimethylformamide.

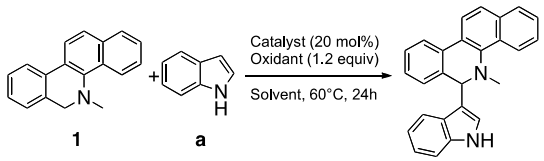
[c]Catalyst (10 mol%).

[d]Base (2.5 equiv).

[e]Reaction carried out in toluene.

[f]Catalyst (30 mol%) and ligand (60 mol%).

Table 2. Optimization for the synthesis of product **2a**.[a]



1 **a** **2a**

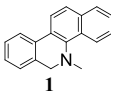
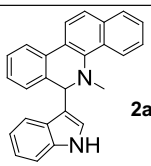
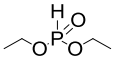
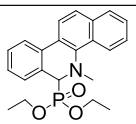
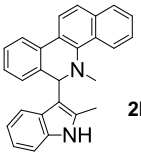
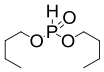
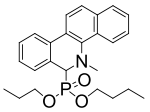
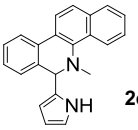
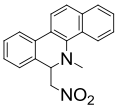
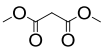
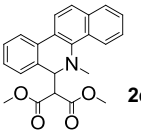
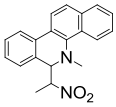
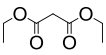
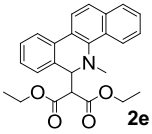
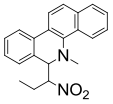
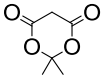
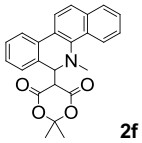
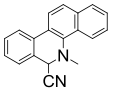
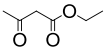
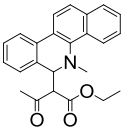
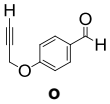
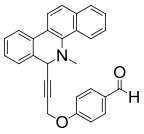
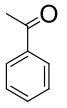
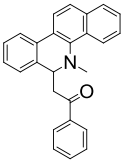
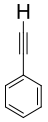
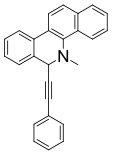
Entry	Catalyst	Oxidant	Solvent	Isolated yields (%)
1	I_2	O_2	DCM:MeOH	-
2	I_2	O_2	MeOH	-
3	$RuCl_3$	O_2	MeOH	20
4	$FeCl_3$	TBHP	DCE	13[b]
5	$FeCl_2$	H_2O_2	MeOH	7
6	-----	DDQ	$PhCH_3$	30
7	CuBr	DDQ	$PhCH_3$	45
8	CuBr	DDQ	CH_3CN:$PhCH_3$	60[c]

[a]Reaction conditions: Compound **1** (1 equiv), compound **a** (1.2 equiv), oxidant (1.2 equiv), catalyst (20 mol%), solvent (0.2 M), 60 °C, 24 h.

[b]2 equiv of TBHP.

[c]Reaction carried out at 80 °C.

Table 3. CDC reaction of DHB (1) with several nucleophiles.

Entry	1	2	Product	Yield [%][b]	Entry	1	2	Product	Yield [%][b]
1	 **1**	 **a**	 **2a**	60	**9**	**1**	 **i**	 **2i**	30
2	**1**	 **b**	 **2b**	56	**10**	**1**	 **j**	 **2j**	41
3	**1**	 **c**	 **2c**	39	**11**	**1**	 **k**	 **2k**	55[d]
4	**1**	 **d**	 **2d**	40[c]	**12**	**1**	 **l**	 **2l**	32[d]
5	**1**	 **e**	 **2e**	40[c]	**13**	**1**	 **m**	 **2m**	25[d]
6	**1**	 **f**	 **2f**	22	**14**	**1**	 **n**	 **2n**	42
7	**1**	 **g**	 **2g**	20	**15**	**1**	 **o**	 **2o**	60
8	**1**	 **h**	 **2h**	18	**16**	**1**	 **p**	 **2p**	70

Reaction conditions: [a]Compound **1** (1 equiv), nucleophile (1.2 equiv), DDQ (1.2 equiv), CuBr (20 mol%), 50:50 v/v CH_3CN:$PhCH_3$ (0.2 M), 80°C, isolated yields in parenthesis. [b] Yields of isolated products based on DHB. [c]Cs_2CO_3 (1.2 equiv.) was added. [d]2 equiv of nucleophile were added.