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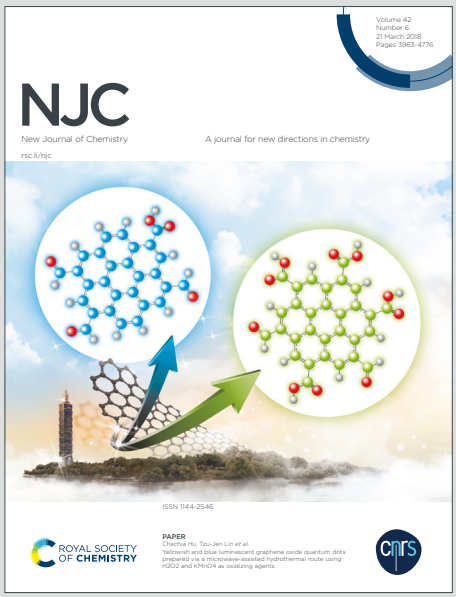

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COMMUNICATION

$AgNO_3$-Catalyzed Decarboxylative Cross-coupling Reaction: An Approach to Coenzyme Q

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An efficient and general method for the synthesis of Coenzyme Q compounds through the activation of 1,4-benzoquinone C_{sp2}-H bond has been developed. This C-C bond formation reaction proceeds readily in an open flask by direct cross-coupling reaction of Coenzyme Q_0 with commercially available aliphatic carboxylic acids utilizing $AgNO_3$ as catalyst and $K_2S_2O_8$ as oxidant in aqueous solution. This radical reaction is operationally simple and amenable to gram-scale synthesis.

Coenzyme Q (CoQ_n), also known as the ubiquinones, is a vitamin-like 1,4-benzoquinone compound and functions as a potent antioxidant that scavenges free radicals.[1] CoQ molecules are acting as mobile mediators for electron transfer and protein translocation between redox enzymes in the electron transport chain of mitochondria.[2] The metabolites of CoQ homologues and a number of synthetic CoQ compounds have been reported possess antineoplastic, anti-inflammatory and antimicrobial activities.[3] CoQ_{10} and idebenone are the most known Coenzyme Q drugs which is widely used in the treatment of Friedreich's ataxia,[4] Alzheimer's disease, Parkinson's disease and mitochondrial disorders.[5] 2,3-Dimethoxy-5-methyl-1,4-benzoquinone, known as Coenzyme Q_0 (CoQ_0), can serve as a key intermediate in the synthesis of coenzyme Q_{10}, idebenone and other CoQ Compounds (**Figure 1.**).[6]

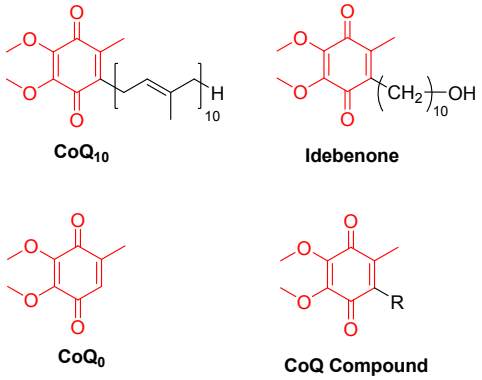

Figure 1. Structures of CoQ_{10}, Idebenone, CoQ_0 and CoQ compound

To date, the most general methods for the preparation of CoQ compounds are starting from 3,4,5-trimethoxytoluene **1** [7] or 2,3,4,5-tetramethoxytoluene **2** [8] through multistep reactions (**Scheme 1a**). These methods involved tedious reaction conditions (Friedel-Crafts, hydrogenation, Heck reaction, etc.), use of toxic reagents or low total yields. Therefore, the development of novel and practical methods for the straightforward synthesis of CoQ compounds are highly desired.

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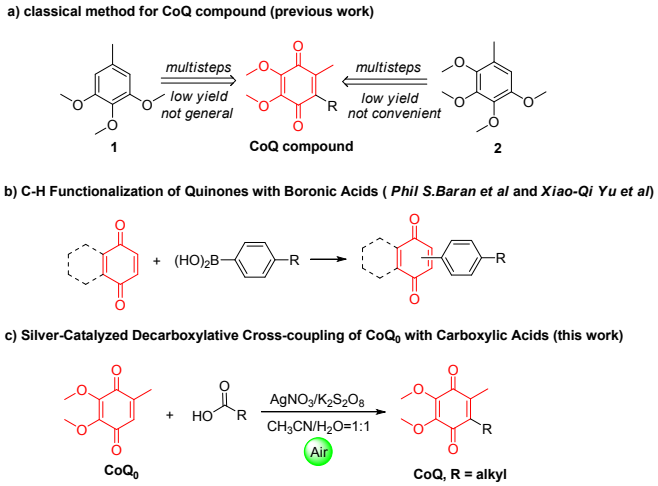
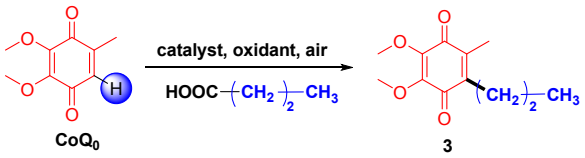


Scheme 1. Various methods for CoQ compound

Arylboronic acids are widely used as cross-coupling reaction partners in the formation of C–C bonds. Baran *et al*[9] and Yu *et al*[10] reported a direct arylation of quinones with boronic acids to afford aryl substituted CoQ compounds (**Scheme 1b**). However, these reactions are time comsuming, and the reagent arylboronic acids are expensive and not easily available. Compared with the boronic acids, the ready availability, high stability, and low cost of aliphatic carboxylic acids are good reagents for the decarboxylative reactions involving the cleavage of C(sp3)–COOH bonds to form a new C-C bond.[11] Following our previous work on synthesis of Coenzyme Q analogues,[12] herein, we report the first direct decarboxylative cross-coupling reaction of CoQ_0 with aliphatic carboxylic acids (**Scheme 1c**).

Our initial trial commenced with the reaction of CoQ_0 and butanoic acid (1.2 equiv) by catalytic $AgNO_3$ (20%) in the presence of $K_2S_2O_8$ (2 equiv). Within 2 h, the reaction was complete and delivered the alkylated CoQ **3** in 43% yield after isolation. (entry 2, **Table 1**). This reaction is operationally simple, is run under air, is clean and scalable. Without the catalyst silver salt, the reaction can not proceed (entry 1, **Table 1**). Examination of various solvents at 80 °C under open air for 2 h revealed that the best reaction solvent is acetonitrile (entry 2, **Table 1**). Several other silver catalysts were screened in the reaction, Ag_2CO_3 and AgOAc catalyzed the reaction with moderate efficiency (entries 9-10,**Table 1**), and $AgNO_3$ was ultimately chosen as the catalyst because it formed CoQ in the best yield. Oxidants $K_2S_2O_8$, $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$, were also examined in the reaction (entries 11-13,**Table 1**), $K_2S_2O_8$ can catalyze this reaction with a best yield (57%, entry11, **Table 1**). The effect of the amount of $AgNO_3$ and $K_2S_2O_8$ was examined, and the results showed that an increase in the amount of $AgNO_3$ and $K_2S_2O_8$ lead to higher conversion of Coenzyme Q_0. (entries 14-17,**Table 1**). The optimal condition was using $AgNO_3$ (40%), and $K_2S_2O_8$ (2 equiv) in acetonitrile at 80 °C for 2 h (entry 15, **Table 1**).

Table 1. Table Silver-catalyzed decarboxylative reaction under different conditions



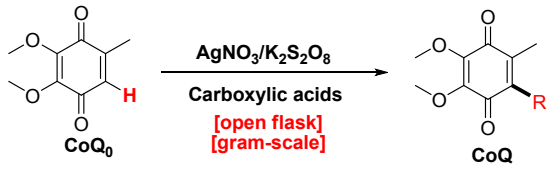
Entry	Catalyst (%)	Oxidant (equiv.)	solvent	Yield (%)
1	none	$K_2S_2O_8$(2)	CH_3CN	0
2	$AgNO_3$(10)	$K_2S_2O_8$(2)	CH_3CN	43
3	$AgNO_3$(10)	$K_2S_2O_8$(2)	THF	20
4	$AgNO_3$(10)	$K_2S_2O_8$(2)	Acetone	10
5	$AgNO_3$(10)	$K_2S_2O_8$(2)	MeOH	0
6	$AgNO_3$(10)	$K_2S_2O_8$(2)	EtOH	0
7	$AgNO_3$(10)	$K_2S_2O_8$(2)	DMSO	Trace
8	$AgNO_3$(10)	$K_2S_2O_8$(2)	DMF	0
9	Ag_2CO_3(10)	$K_2S_2O_8$(2)	CH_3CN	20
10	AgOAc(10)	$K_2S_2O_8$(2)	CH_3CN	32
11	$AgNO_3$(20)	$K_2S_2O_8$(2)	CH_3CN	57
12	$AgNO_3$(20)	$(NH_4)_2S_2O_8$(2)	CH_3CN	Trace
13	$AgNO_3$(20)	$Na_2S_2O_8$(2)	CH_3CN	50
14	$AgNO_3$(30)	$K_2S_2O_8$(2)	CH_3CN	64
15	**$AgNO_3$(40)**	**$K_2S_2O_8$(2)**	**CH_3CN**	**75**
16	$AgNO_3$(50)	$K_2S_2O_8$(3)	CH_3CN	70
17	$AgNO_3$(60)	$K_2S_2O_8$(3)	CH_3CN	60

Reaction Conditions: CoQ_0 (0.02mol), butanoic acid (1.2 equiv), 80 °C, 2 hour under open air

With the optimum reaction conditions in hand, we explored the substrate scope with regard to different carboxylic acid (**Table 2**). Delightfully, the substrate scope is quite general, comercial availbale long-chain carboxylic acids can be applied to this protocol, thus affording the corresponding CoQ compounds in good to excellent yields (entry 1-3, **Table 2**). It was interesting to note that a CoQ drug idebenone (**6**) was obtained in gram-scale by the reaction of 11-Hydroxyundecanoic acid with CoQ_0 in 75% yield with no by-product (entry 3, **Table 2**). However, when use the short carbon chains acetic acid or benzoic acid as coupling

reaction partners to react with CoQ_0 under the same conditions, low yield of CoQ product were observed (entry 4-5, **Table 2**).

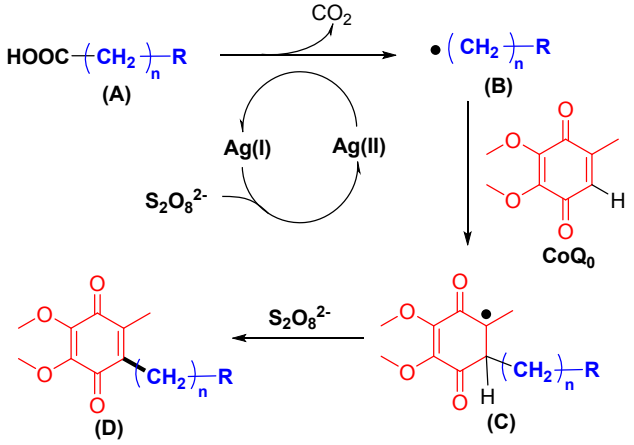
Table 2. Cross-coupling of Coenzyme Q_0 with carboxylic acids



Entry	Carboxylic acids	R	CoQ	Yield (%)
1	HOOC-$(CH_2)_8$-CH_3	$(CH_2)_8$-CH_3	**(4)**	80
2	HOOC-$(CH_2)_9$-OH	$(CH_2)_9$-OH	**(5)**	70
3	**HOOC-$(CH_2)_{10}$-OH**	**$(CH_2)_{10}$-OH**	**(6)**	**75**
4	HOOC-CH_3	CH_3	**(7)**	trace
5	HOOC-Ph	Ph	**(8)**	5

Reaction Conditions: CoQ_0 (0.02mol), carboxylic acid (1.5 equiv), $AgNO_3$ (40%), $K_2S_2O_8$ (2 equiv)

Based on the experiment results, a silver-catalyzed decarboxylative decarboxylative C_{sp2}-H cross-coupling reaction is tentatively illustrated in **Scheme 2**. Initially, Ag(I) was oxidized into Ag(II) inermediate by $S_2O_8^{2-}$ and the carboxylic acids **(A)** underwent an SET process to generate the corresponding carbon radical **(B)** and release CO_2.[13-14] The carbon radical **(B)** then attack the C_{sp2}-H of CoQ_0 to afford intermediate **(C)**, which can transfer to the product idebenone **(D)** by $S_2O_8^{2-}$.



Scheme 2. Proposed reaction mechanism

In conclusion, we have developed a practical and convenient synthesis of Coenzyme Q compounds by the use of catalytic silver-(I) nitrate in the presence of $K_2S_2O_8$ as co-oxidants. This decarboxylative C-C cross-coupling reaction between CoQ_0 and aliphatic carboxylic acids proceed well under open air conditions. This method is easily operational, mild and efficient. It has been applied to the gram-scale synthesis of CoQ drug idebenone (**6**) with a yield of 75%, which makes the method highly applicable. This chemistry provided a novel C_{sp2}-H alkylation approach leading to other alkylated CoQ compounds which are of high synthetic value. Studies on the applications in natural CoQ syntheses are ongoing in our laboratory.

Experimental Section

Synthesis of CoQ compounds

To a solution of Coenzyme Q_0 (3.64 g, 0.02 mol) and carboxylic acids (0.03mol) in acetonitrile 80 mL was added $AgNO_3$ (1.35 g, 8 mmol). The mixture was heated to 80 °C and a solution of $K_2S_2O_8$ (10.81 g, 0.04 mol) in distilled water 80 mL was added dropwise over 2 h, then the reaction mixture was stirred for another 2 h, with TLC monitoring unitil the starting material was consumed. The resulting mixture was cooled and extracted with CH_2Cl_2. The organic layer was washed with water, then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatograph on silica gel (PE/EtOAc= 5:1) to give CoQ compounds.

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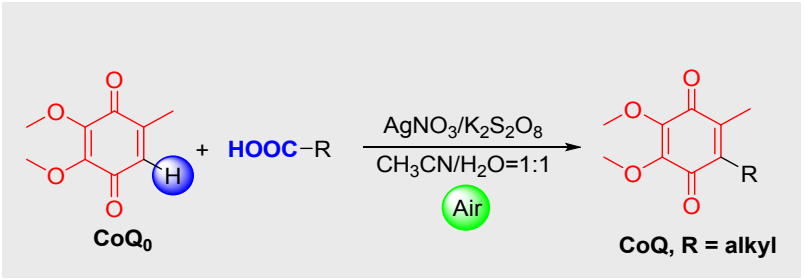
$AgNO_3$-Catalyzed Decarboxylative Cross-coupling Reaction: An Approach to Coenzyme Q



- ✓ high yields
- ✓ gram-scale synthesis
- ✓ C_{sp2}-H functionalization
- ✓ Decarboxylative Cross-coupling