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Synthetic Methods

Copper-Catalyzed Dehydrogenative Cross-Coupling Reaction between Allylic C–H Bonds and α-C–H Bonds of Ketones or Aldehydes

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Abstract: A dehydrogenative cross-coupling reaction between allylic C–H bonds and the α-C–H bond of ketones or aldehydes was developed using $Cu(OTf)_2$ as a catalyst and DDQ as an oxidant. This synthetic approach to γ,δ-unsaturated ketones and aldehydes has the advantages of broad scope for both ketones and aldehydes as reactants, mild reaction conditions, good yields and atom economy. A plausible mechanism using $Cu(OTf)_2$ as a Lewis acid catalyst was also proposed (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Tf = trifluoromethanesulfonate).

Transitional metal-catalyzed allylic alkylation, especially palladium-,[1] copper-,[2] or molybdenum-catalyzed[3] allylic alkylation, has become a powerful method for C–C bond formation in recent decades. Typically, good leaving groups are required in the allylic position, such as acetoxy, halo, amino, hydroxy or carbonate groups.[1–3] To avoid prefunctionalization of the substrates, Tsuji and others performed these reactions through allylic C–H activation rather than allylic functional group cleavage since the 1960 s.[4] However, two-step protocols are required in the allylic C–H alkylation mediated by stoichiometric Pd^{II}.[4,5b]

After nearly half a century, a few methods have been developed to reduce the above two-step procedure into a single operation through dehydrogenative cross-coupling (DCC) reactions,[5] which is considered a new generation of C–C bond formations.[6] In 2006, Li et al. pioneered the allylic C–H alkylation with 1,3-diketones or β-keto esters through DCC reactions using $CuBr_2$ and $CoCl_2$ as catalysts.[5a] In 2008, Shi's group developed an intra/intermolecular allylic alkylation of C–H bonds with 1,3-diketones as nucleophiles by using a $Pd(OAc)_2$/1,2-bis(phenylsulfinyl) ethane/BQ system (BQ = 1,4-benzoquinone).[5b] Efficient DCC reactions between allylic C–H bonds and the C–H bonds of α-nitro esters or α-nitro ketones under palladium catalysis were also reported by White et al.[5c–d] In 2008, Bao and co-workers developed an allylic alkylation with 1,3-dicarbonyl compounds promoted by DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[5e] In 2012, Trost et al. unveiled that 1,4-diene performed allylic alkylation smoothly with active methylene compounds as nucleophiles using $Pd(OAc)_2/Ph_3P$ as a catalyst and 2,6-DMBQ as an oxidant (DMBQ = dimethoxybenzoquinone).[5f] Very recently, Trost's group also discovered an enantioselective allylic C–H alkylation with 1,3-diketones under palladium catalysis through DCC reaction.[5g]

Despite the elegance of these methods, the nucleophiles are mainly limited to active methylene compounds, such as 1,3-diketones, β-keto esters, α-nitro esters, α-nitro ketones, and nitro compounds. To the best of our knowledge, allylic C–H alkylation with common ketones or aldehydes remains unknown. Considering that ketones or aldehydes are less reactive than active methylene compounds as carbon-nucleophiles, we envision to use a Lewis acid catalyst to activate ketones or aldehydes to promote the allylic C–H alkylation. Herein we wish to present our recent results on Lewis acid catalyzed DCC reaction between allylic C–H bonds and the α-C–H bond of ketones or aldehydes.

Initially, cyclohexanone **1 a** and 1,3-diphenylpropene **2** were chosen as model substrates to optimize the DCC reaction. To our delight, when $ZnCl_2$ and DDQ were employed as a Lewis acid and an oxidant, respectively, in CH_2Cl_2 at room temperature, the desired coupling product, γ,δ-unsaturated ketone **3 a** was obtained, albeit in a low yield (Table 1; entry 1). Other Lewis acids were then probed in the reaction (see the Supporting Information). The acidity of $AlCl_3$ seemed too strong for this DCC reaction, and no desired coupling product **3 a** was observed (Table 1; entry 2). $Cu(OTf)_2$ proved to be the best catalyst with regard to the yield of **3 a** (Table 1; entry 3). The increase of the load of $Cu(OTf)_2$ catalyst seemed to be not beneficial to the reaction (Table 1; compare entry 3 with entries 4 and 5). Other oxidants except DDQ, such as *tert*-butylhydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), and *meta*-chloroperbenzoic acid (*m*-CPBA), were hardly effective in the reaction (Table 1; entries 6–8). Various solvents were also examined, and CH_3CN resulted in the best yield (Table 1; compare entries 3, 9–11 with 12). In further exploration, when 1.5 equivalents of H_2O was added, the yield of **3 a** was increased to 75 % (Table 1; entry 13).[7] Raising the reaction temperature from room temperature to 85 °C led to the reduction of the yield (Table 1;

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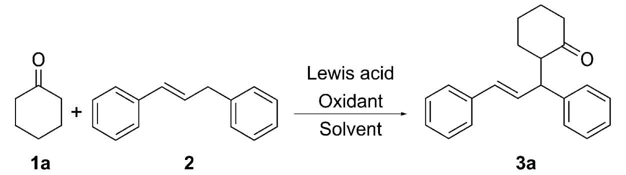
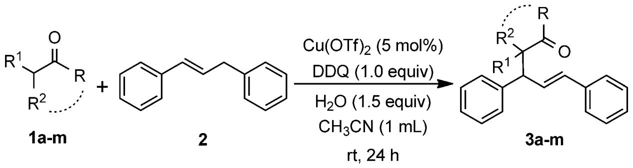
Table 1. Optimization of DCC reaction between cyclohexanone **1a** and 1,3-diphenylpropene **2**.[a]

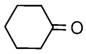
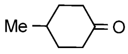
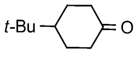
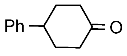
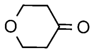
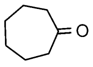
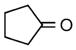
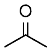
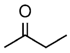
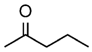
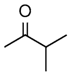
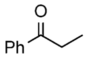
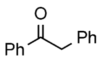


Entry	Lewis acid [(mol%)]	Oxidant [(equiv)]	Solvent	Yield [%][b]
1	$ZnCl_2$(10)	DDQ(1)	CH_2Cl_2	15
2	$AlCl_3$(5)	DDQ(1)	CH_2Cl_2	NP
3[c]	Cu(OTf)$_2$(5)	DDQ(1)	CH_2Cl_2	38
4[c]	Cu(OTf)$_2$(10)	DDQ(1)	CH_2Cl_2	35
5[c]	Cu(OTf)$_2$(20)	DDQ(1)	CH_2Cl_2	33
6	Cu(OTf)$_2$(5)	TBHP(3)	CH_2Cl_2	NP
7	Cu(OTf)$_2$(5)	DTBP(3)	CH_2Cl_2	NP
8	Cu(OTf)$_2$(5)	*m*-CPBA(1)	CH_2Cl_2	NP
9	Cu(OTf)$_2$(5)	DDQ(1)	DCE	30
10	Cu(OTf)$_2$(5)	DDQ(1)	$CHCl_3$	45
11[c]	Cu(OTf)$_2$(5)	DDQ(1)	$MeNO_2$	46
12[c]	Cu(OTf)$_2$(5)	DDQ(1)	CH_3CN	55
13[d]	Cu(OTf)$_2$(5)	DDQ(1)	CH_3CN	75
14[d,e]	Cu(OTf)$_2$(5)	DDQ(1)	CH_3CN	57
15[d,g]	Cu(OTf)$_2$(5)	DDQ(1)	CH_3CN	86

[a] The mixture of **1a** (0.6 mmol), **2** (0.3 mmol), and DDQ (0.3 mmol) in solvent (1 mL) was stirred at room temperature for 24 h; [b] Isolated yield; [c] Reaction completed in 2 h; [d] 1.5 equivalents of H_2O was added. Reaction completed in 24 h; [e] 85 °C; [g] DDQ was added in three portions at 0 °C for 1.5 h, and the resulting mixture was stirred for 24 h at room temperature.

Table 2. DCC reaction between ketones **1a–m** and 1,3 diphenylpropene **2**.[a]



Entry	Ketone		Product	Yield [%][b]
1		**1a**	**3a**	86
2		**1b**	**3b**	87
3		**1c**	**3c**	90
4		**1d**	**3d**	95
5		**1e**	**3e**	84
6		**1f**	**3f**	65
7		**1g**	**3g**	77
8		**1h**	**3h**	88
9		**1i**	**3i**	87
10		**1j**	**3j**	82
11		**1k**	**3k**	89
12		**1l**	**3l**	68
13		**1m**	**3m**	62

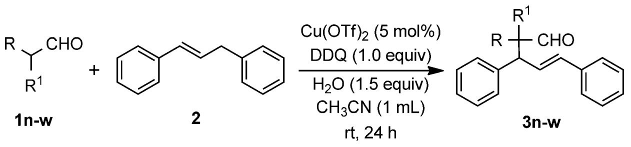
[a] Reaction conditions: ketone **1** (0.6 mmol), **2** (0.3 mmol), Cu(OTf)$_2$ (5 mol%), DDQ (0.3 mmol), CH_3CN (1 mL), room temperature, 24 h; [b] Isolated yield, d.r. (*anti*/*syn*) ≈ 1:1.

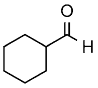
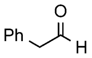
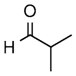
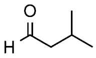
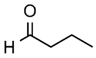
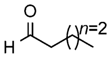
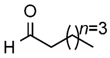
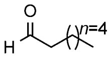
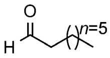
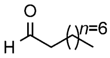
entry 14). If DDQ was added in three portions at 0 °C for 1.5 h, the yield was further increased to 86% after stirring for 24 h at room temperature (Table 1; entry 15). It was noteworthy that, in the absence of Cu(OTf)$_2$, no **3a** was obtained. Thus, it can be concluded that the optimized reaction should be performed under the catalysis of 5 mol% Cu(OTf)$_2$ in the presence of 1.0 equivalent of DDQ and 1.5 equivalents H_2O at room temperature in CH_3CN.

With the optimized conditions in hand, the scope of the DCC reaction was examined. We were pleased to find that various substituted cyclohexanones **1b–d** underwent the reaction smoothly to give the desired γ,δ-unsaturated ketones **3b–d** in excellent yields (Table 2; entries 2–4). Tetrahydropyran-4-one **1e**, which bore a strong electron-withdrawing oxygen atom on the ring, also performed well in the reaction (Table 2; entry 5). Expanding or compressing the size of cyclic ketone **1a** led to significant reductions of yields (Table 2; compare entry 1 with entries 6 and 7). The straight-chain ketone as simple as acetone **1h** performed the reaction smoothly to give coupling product **3h** in an excellent yield (Table 2; entry 8). The reaction was highly regioselective for the unsymmetric ketones **1i** and **j**, and the C–C bonds formed at more substituted α-carbon of ketones **1i** and **j** to give the corresponding products **2i** and **j** (Table 2; entries 9 and 10). The results are consistent with the formation of a more stable enol under Lewis acid catalysis. Similarily, although the carbon in 3-position of 3-methylbutan-2-one **1k** is more hindered as compared to that in 1-position, **1k** still led to γ,δ-unsaturated ketone **3k** with forming a quaternary carbon in an excellent yield (Table 2; entry 11). Besides aliphatic ketones, aromatic ketones also performed the DCC reaction expediently. Both 1-phenylpropanone **1l** and 1,2-diphenylethanone **1m** resulted in the corresponding γ,δ-unsaturated ketones **3l** and **m** in satisfactory yields (Table 2; entries 12 and 13).

Moreover, various aldehydes were also examined in the DCC reaction under the optimized conditions. It was found that cyclohexanal **1n** and phenyl acetaldehyde **1o** performed the reaction smoothly to give the corresponding coupling products **3n** and **o** in 90 and 93% yield, respectively (Table 3; entries 1 and 2). Similar to α-alkyl substituted ketone **1k**, α-alkyl substituted aldehyde **1p** led to the γ,δ-unsaturated aldehyde **3p** in a good yield with forming a quaternary carbon (Table 2;

Table 3. DCC reaction between aldehydes **1n**–**w** and 1,3-diphenylpropene **2**.[a]

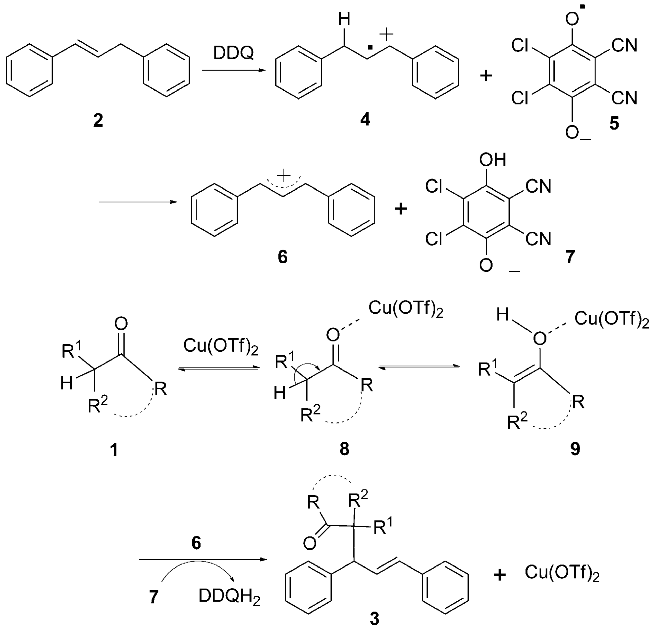


Entry	Aldehyde		Product	Yield [%][b]
1		**1n**	**3n**	90
2		**1o**	**3o**	93
3		**1p**	**3p**	88
4		**1q**	**3q**	80
5		**1r**	**3r**	75
6		**1s**	**3s**	85
7		**1t**	**3t**	73
8		**1u**	**3u**	80
9		**1v**	**3v**	77
10		**1w**	**3w**	75

[a] Reaction conditions: **1** (0.6 mmol), aldehyde **2** (0.3 mmol), $Cu(OTf)_2$ (5 mol%), DDQ (0.3 mmol), CH_3CN (1 mL), room temperature, 24 h; [b] Isolated yield, d.r. (*anti/syn*) ≈ 1:1.

entry 3). A series of straight-chain aldehydes **1r**–**w** were suitable to the DCC reaction, affording γ,δ-unsaturated aldehydes **3r**–**w** in good yields (Table 3; entries 5–10).

Our experiment also demonstrated that when *tert*-butyldimethylchlorosilane (TBSCl) was employed instead of $Cu(OTf)_2$, the DCC reaction of ketone **1a** with 1,3-diphenylpropene **2** also occurred in the presence of DDQ.[8] Thus, under the optimized conditions, DDQ rather than $Cu(OTf)_2$ should result in the formation of positive allylic species.[5e] Similar to TBSCl, $Cu(OTf)_2$ should function as a Lewis acid to promote the enolization of ketone **1** in this reaction. A plausible mechanism for the DCC reaction is depicted in Scheme 1. First, an electron in the C–C double bond of 1,3-diphenylpropene **2** is transferred to DDQ to form a radical cation **4** and a DDQ radical anion **5**. Then, an allylic hydrogen atom is abstracted by the DDQ radical anion **5** to generate an allylic cation **6** and a DDQH anion **7**. At the other hand, ketone **1** coordinates with $Cu(OTf)_2$ to form complex **8**, followed by its keto-enol tautomerization to form copper-complexed enol **9**.[9] The result that the DCC reaction is probably through a more stable enol intermediate (Table 2; entries 9–11) supports that $Cu(OTf)_2$ as a Lewis acid activates ketone **1** to form an enol. Afterwards, enol **9** attacks allylic cation **6** to form coupling product **3**, regenerate $Cu(OTf)_2$, and generate a proton, which is received by DDQH anion **7** to form $DDQH_2$.



Scheme 1. Plausible mechanism of the DCC reaction between ketones or aldehydes **1** and 1,3-diphenylpropene **2**.

In conclusion, we have developed a novel dehydrogenative cross-coupling reaction of common ketones or aldehydes with 1,3-diphenylpropene by using $Cu(OTf)_2$ as a catalyst and DDQ as an oxidant. It is the first example of DCC reaction between allylic C–H bonds and the α-C–H bond of ketones or aldehydes. This synthetic approach to γ,δ-unsaturated ketones and aldehydes has the advantages of broad scope for both ketones and aldehydes as reactants, mild reaction conditions, good yields and atom economy, which makes it practical in future applications. A plausible mechanism using $Cu(OTf)_2$ as a Lewis acid catalyst to activate ketone or aldehyde was also proposed. The DCC reactions of other allylic compounds with aldehydes or ketones under Lewis acid catalysis and their mechanisms are currently under way.

Experimental Section

General Procedure for the DCC Reaction of Ketones or Aldehydes 1 with 1,3-Diphenylpropene 2

To a mixture of $Cu(OTf)_2$ (5.4 mg, 0.015 mmol) in CH_3CN (1 mL), were added 1,3-diphenylpropene **2** (58.2 mg, 0.3 mmol), ketone or aldehyde **1** (0.6 mmol) and H_2O (8.1 mg, 0.45 mmol) in sequence. At 0 °C, the resulting mixture was stirred to become a solution. Then, DDQ (68.1 mg, 0.3 mmol) was added in three portions within 1.5 h. After that, the reaction mixture was stirred for 24 h at room temperature. Then the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether = 1:100 or 1:200 as eluent) to give the desired product **3**.

Acknowledgements

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Keywords: aldehyde · allylic · C–H bonds · coupling reactions · ketones

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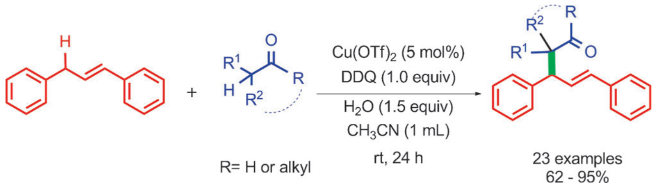

A lovely couple: The first example of a dehydrogenative cross-coupling reaction between allylic C–H bonds and the α-C–H bond of ketones or aldehydes was developed using Cu(OTf)$_2$ as a catalyst and DDQ as an oxidant (see scheme; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Tf = trifluoromethanesulfonate).

Synthetic Methods

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■■–■■

Copper-Catalyzed Dehydrogenative Cross-Coupling Reaction between Allylic C–H Bonds and α-C–H Bonds of Ketones or Aldehydes