One-Pot Access to Cinnamates via Direct Oxidative C–H Transformation of Allylarenes

Meng-Yang Chang,* Shin-Ying Lin, Chieh-Kai Chan

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan
Fax +886(7)3125339; E-mail: mychang@kmu.edu.tw

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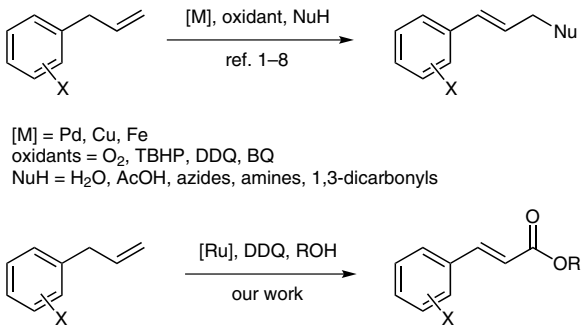
Abstract: A highly selective combination of ruthenium complex and oxidant, which catalyzes the oxidative C–H esterification of allylarenes to the corresponding bis-(*E*)-cinnamates and (*E*)-cinnamates, is described. The one-pot route was carried out by olefinic migration of allylarenes with $RuCl_2(PPh_3)_3$ and DDQ-mediated allylic oxidation of the resulting internal alkenes with various alcohols in good yields.

Key words: allylarenes, C–H esterification, cinnamates

For the selective transition-metal-promoted oxidative functionalization of catalytic C(sp^3)–H bond activation,[1] the specific allylic transformation of allylarenes has been installed as the various allylic C(sp^3)–H functionalized derivatives in these important synthetic protocols and applications, for example, aldehydes,[2] ketones,[3] amines,[4] nitriles,[5] alkanes,[6] acetates,[7] and arenes.[8] In particular, the stereospecific allylic C–H activation of allylarenes using catalysts based on Pd,[1–8] Fe,[5] and Cu[5] having diversified nucleophiles and different oxidants gives the corresponding allylic molecules (Scheme 1).



Scheme 1 Direct transformation from allylarenes to allylic derivatives via C(sp^3)–H functionalization

Among the most synthetic approaches for allylic C(sp^3)–H bond activation, one-pot and direct double esterification of a bisallylarene skeleton via the combination of a $RuCl_2(PPh_3)_3$ catalyst and DDQ oxidant (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) using alcohols as the nucleophiles has not been reported. In continuation of our recent investigation with the starting material 4,4′-bisphenol (**1**) for synthesizing the structural skeleton of polyphenyls, bisdihydrobenzofurans, benzo[*j*]fluoranthen-12-ones),[9] the one-pot domino synthetic route for preparing bis-(*E*)-cinnamate **3a** is described from the direct double esterification of bisallylbenzene **2a** with different conditions, as shown in Table 1. To trigger the synthetic work of skeleton **3**, 3,3′-diallyl-4,4′-bisbenzyloxybiphenyl (**2a**) was first chosen as the starting substrate in the investigation of the direct oxidative C–H transformation of the terminal alkene and it could be prepared from 4,4′-bisphenol (**1**) via a three-step known procedure of O-allylation, Claisen rearrangement, and O-benzylation).[9c]

Next, when we initially employed oxygen as an oxidant for the $PdCl_2(MeCN)_2$-mediated treatment of **2a** with MeOH in CH_2Cl_2, only <5% yield of **3a** was isolated. Internal olefin **4** was obtained as the major product (70%), and **2a** was recovered in 20% yield (Table 1, entry 1). Changing the oxidant to six equivalents of *tert*-butyl hydroperoxide, we found that **3a** (20%), **4** (50%), and **5** (15%) were obtained via a tandem process of olefin migration and then oxidative esterification or bond cleavage. Compound **2a** was also recovered with a 10% yield (Table 1, entry 2). Next, the reaction was treated with cerium ammonium nitrate (CAN, 6 equiv); **3a** (36%), **4** (38%), and **5** (20%) were provided in similar product distribution (Table 1, entry 3). Furthermore, when the oxidant was replaced with DDQ (10 equiv),[10] the yield of the desired **3a** was increased to 48%, and **6** was isolated with a 14% yield (Table 1, entry 4). Compund **5** was determined by single-crystal X-ray crystallography.[11] After increasing the catalytic amounts of $PdCl_2(MeCN)_2$ and changing the reaction solvent (CH_2Cl_2, DCE, toluene) and volume (10 or 20 mL), **3a** provided similar yields (70–76%, Table 1, entries 5–10). To our delight, changing the catalyst from $PdCl_2(MeCN)_2$ to $RuCl_2(PPh_3)_3$,[12] **3a** provided better yields (80–90%) for entries 11–15 (Table 1). According to the above-mentioned synthetic procedure, we envisioned that the optimized one-pot esterification conditions should involve the one-pot synthesis of bis-*o*-allylbenzene with alcohol via the combination of $RuCl_2(PPh_3)_3$ (10 mol%), DDQ (10 equiv), and CH_2Cl_2 (10 mL).

So far, there are fewer examples to describe the one-pot and direct oxidative esterification of **2** bearing the allylic C–H bond with alcohols by $RuCl_2(PPh_3)_3$ and DDQ under air atmosphere.[10i,13] The product **3a** was confirmed through ^{1}H NMR analysis. It exhibited two doublets at δ = 8.10 and 6.62 ppm for olefinic CH protons. One CH_2 proton appeared as one singlet of methylene (δ = 5.20) and the other CH_3 singlet of the methyl ester group appeared

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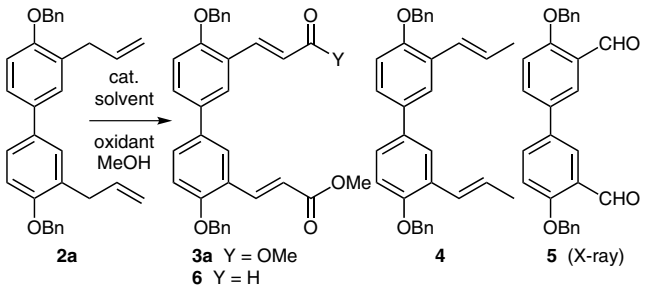
at δ = 3.80 ppm. However, the related resolutions of the *meso* and dl isomers were not observed from the NMR spectrum. Perhaps the given distance between the two conjugated esters was so long that the free rotation of the side-chain arms in between easily resulted.

Table 1 Allylic C–H Bond Transformation of **2a**[a–f]

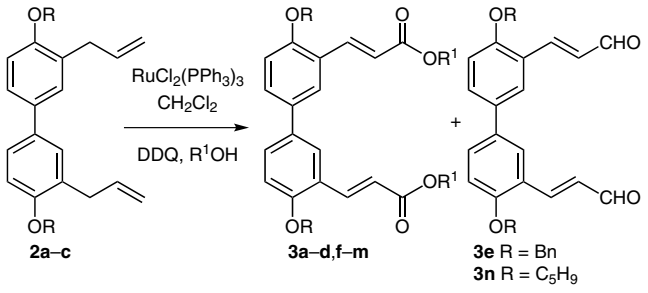


Entry	Catalyst (mmol%), Solvent (mL), Oxidant (equiv)	Yield (%)[b]
1	$PdCl_2(MeCN)_2$ (2), CH_2Cl_2 (10), O_2	<5[c]
2	$PdCl_2(MeCN)_2$ (2), CH_2Cl_2 (10), *t*-BuO_2H (6)	20[d]
3	$PdCl_2(MeCN)_2$ (2), CH_2Cl_2 (10), CAN (6)	30[e]
4	$PdCl_2(MeCN)_2$ (2), CH_2Cl_2 (10), DDQ (4)	48[f]
5	$PdCl_2(MeCN)_2$ (2), CH_2Cl_2 (10), DDQ (10)	76
6	$PdCl_2(MeCN)_2$ (5), CH_2Cl_2 (10), DDQ (10)	75
7	$PdCl_2(MeCN)_2$ (10), CH_2Cl_2 (10), DDQ (10)	75
8	$PdCl_2(MeCN)_2$ (10), $(CH_2Cl)_2$ (10), DDQ (10)	72
9	$PdCl_2(MeCN)_2$ (10), toluene (10), DDQ (10)	72
10	$PdCl_2(MeCN)_2$ (10), CH_2Cl_2 (20), DDQ (10)	70
11	$RuCl_2(PPh_3)_3$ (5), CH_2Cl_2 (10), DDQ (6)	80
12	$RuCl_2(PPh_3)_3$ (5), CH_2Cl_2 (10), DDQ (10)	83
13	$RuCl_2(PPh_3)_3$ (10), CH_2Cl_2 (10), DDQ (10)	90
14	$RuCl_2(PPh_3)_3$ (10), DCE (10), DDQ (10)	82
15	$RuCl_2(PPh_3)_3$ (10), toluene (10), DDQ (10)	80

[a] All reactions were run with **2a** (120 mg, 0.4 mmol), catalyst (2–10 mmol%), CH_2Cl_2 (10–20 mL), MeOH (1 mL), and oxidants (1.6–4.0 mmol) at reflux.
[b] Th product **3a** was >95% pure as determined by ^1H NMR analysis.
[c] Compound **4** was isolated with 70% yield, and 20% of **2a** were recovered.
[d] Compounds **4** (50%), **5** (15%), and **2a** (10%) were obtained.
[e] Compounds **4** (38%) and **5** (20%) were obtained.
[f] Compound **6** (14%) was isolated.

Changing the substitutent of **2** (**2a** R = Bn, **2b** R = Me, **2c** R = C_5H_9), **3a**–**n** were isolated with 83–92% yield by one-pot oxidative $RuCl_2(PPh_3)_3$/DDQ-mediated allylic esterification of **2** with five alcohols (MeOH, EtOH, *i*-PrOH, $EtOCH_2CH_2OH$, and *t*-BuOH) in CH_2Cl_2 at reflux for three hours (Table 2). When treatment of **2a** or **2c** reacted with tertiary alcohol (*t*-BuOH, Table 2, entries 5 and 14), we observed that biscinnamaldehyde **3e** or **3n** replaced the expected bi-*tert*-butyl biscinnamate with 83% or 85% yield. This phenomenon showed that the *tert*-butyl group was so bulky that it could not attack the in situ generated cinnamaldehyde to form the desired skeleton of biscinnamate **3**.

Table 2 Synthesis of **3**[a,b]



Entry	Reactants **2**	R^1OH	Yield of **3** (%)[b]
1	**2a** R = Bn	MeOH	**3a** 90
2	**2a** R = Bn	EtOH	**3b** 88
3	**2a** R = Bn	*i*-PrOH	**3c** 80
4	**2a** R = Bn	$EtOCH_2CH_2OH$	**3d** 87
5	**2a** R = Bn	*t*-BuOH	**3e** 83
6	**2b** R = Me	MeOH	**3f** 92
7	**2b** R = Me	EtOH	**3g** 90
8	**2b** R = Me	*i*-PrOH	**3h** 84
9	**2b** R = Me	$EtOCH_2CH_2OH$	**3i** 90
10	**2c** R = C_5H_9	MeOH	**3j** 92
11	**2c** R = C_5H_9	EtOH	**3k** 90
12	**2c** R = C_5H_9	*i*-PrOH	**3l** 86
13	**2c** R = C_5H_9	$EtOCH_2CH_2OH$	**3m** 90
14	**2c** R^1 = C_5H_9	*t*-BuOH	**3n** 85

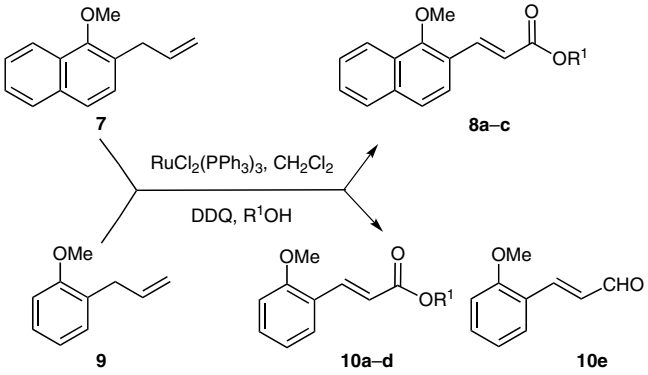
[a] All reactions were run with **2** (0.4 mmol), $RuCl_2(PPh_3)_3$ (10 mmol%), CH_2Cl_2 (10 mL), alcohols (R^1OH, 1 mL), and DDQ (900 mg, 4.0 mmol) at reflux.
[b] Compounds **3a**–**n** were >95% pure as determined by ^1H NMR analysis.

We extend this useful protocol to 2-allyl-1-methoxynaphthalene (**7**), which was prepared from Claisen rearrangement of 1-allyloxynaphthalene followed by O-methylation from the intermediate 1-naphthol. We found that products **8a**–**c** were easily formed as the sole isomers with 82–90% yield by the combination of $RuCl_2(PPh_3)_3$/DDQ with different types of alcohol. Under the same conditions, attempts to apply the protocol for 1-allyl-2-methoxybenzene (**9**) were also successful. Compounds **10a**–**e** were obtained in high yield (86–90%), as shown in Table 3.

How is **10a** produced?[2,5] As shown in Scheme 2, the initial event for the ruthenium-catalyzed migration of **9** may be

considered as the formation of intermediates **A** and **B** via the equilibrium by [3,3]-sigmatropic rearrangement.[14] Intermediate **B** should exist as the major state through the chelated Ru-complex. Furthermore, intermediate **B** is subjected to the regioselective nucleophilic attack of MeOH to afford intermediate **C** from a less hindering site. Finally, product **10a** is subsequently formed through allylic oxidation of intermediate **C** with DDQ and molecular oxygen (from air) followed by dehydroxylative oxidation of intermediate **D**.[15,16] Ru(0) is oxidized to generate active Ru(II) by excess amounts of DDQ. From the possible reaction mechanism, we believe that excess DDQ plays an important dual functional role between activating Ru(0) and allylic C–H bonds during the one-pot direct oxidative transformation.

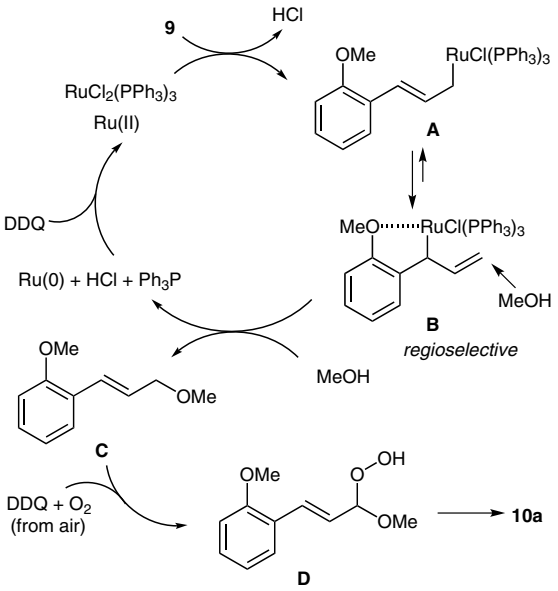
Table 3 Synthesis of **8** and **10**[a,b]



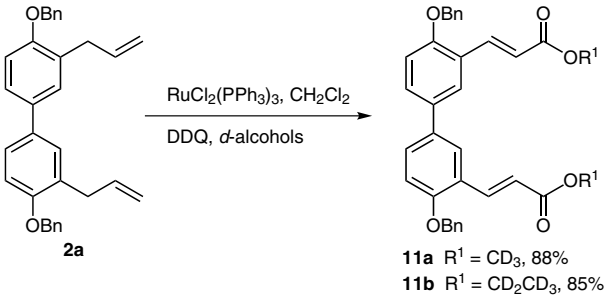
Entry	Reactants **7** and **9**	R^1OH	Yields of **8** and **10** (%)[b]
1	**7**	MeOH	**8a** 82
2	**7**	*i*-PrOH	**8b** 90
3	**7**	$EtOCH_2CH_2OH$	**8c** 83
4	**9**	MeOH	**10a** 88
5	**9**	EtOH	**10b** 86
6	**9**	*i*-PrOH	**10c** 90
7	**9**	$EtOCH_2CH_2OH$	**10d** 86
8	**9**	*t*-BuOH	**10e** 86

[a] All reactions were run with **7** or **9** (0.4 mmol), $RuCl_2(PPh_3)_3$ (10 mmol%), CH_2Cl_2 (10 mL), alcohols (R^1OH, 1 mL), and DDQ (450 mg, 2.0 mmol) at reflux.
[b] Compounds **8a–c** or **10a–e** were >95% pure as determined by ^1H NMR analysis.

Under $RuCl_2(PPh_3)_3$/DDQ conditions, reactions for **2a** with CD_3OD and C_2D_5OD were further studied, as shown in Scheme 3. By controlling the R^1 group of alcohols (a, MeOH-*d*; b, EtOH-*d*), the desired biscinnamates **11a**,**b** with the deuterium group were only isolated with 80–88% yields. We believe that the presented experimental results should provide a potential application for isotope chemistry.



Scheme 2 Proposed reaction mechanism of the direct transformation for **10a**[2,5]



Scheme 3 Synthesis of **11**

In summary, we have successfully presented a synthetic methodology for different alkyl cinnamates **8** and **10**, and biscinnamates **3**, which involve one-pot oxidative esterification of skeletons **2**, **7**, and **9** with the combination of $RuCl_2(PPh_3)_3$/DDQ in good yield. The novel allylic C–H bond route showed that $RuCl_2(PPh_3)_3$ is an excellent catalyst source to promote the formation of the olefinic migration, and that DDQ is an oxidant for mono and double allylic esterification. Considering the utility of the skeleton of 4,4′-bisphenol (**1**), the development of these facile and novel synthetic approaches is significant.

Acknowledgment

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(11) CCDC 896676 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

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(13) **Representative Synthetic Procedure of Skeletons 3, 8, and 10**
$RuCl_2(PPh_3)_3$ (38 mg, 0.04 mmol) was added to a solution of skeleton **2**, **7**, or **9** (0.4 mmol) in CH_2Cl_2 (10 mL) at reflux for 2 h. The reaction mixture was cooled to r.t. Then alcohols (1 mL) and DDQ (for skeleton **2**: 900 mg, 4.0 mmol; for skeleton **7** or **9**: 450 mg, 2.0 mmol) were added to the reaction mixture. The reaction mixture was stirred at reflux for 1 h. The reaction mixture was cooled to r.t. The residue was diluted with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes–EtOAc = 10:1 to 6:1) afforded skeletons **3**, **8**, and **10**.

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