Published in final edited form as:

European J Org Chem. 2015 March ; 2015(9): 1899–1904. doi:10.1002/ejoc.201403518.

Synthesis of 2-Acylphenol and Flavene Derivatives from the Ruthenium-Catalyzed Oxidative C–H Acylation of Phenols with Aldehydes

Hanbin Lee and Prof. Dr. Chae S. Yi^[a]

Chae S. Yi: chae.yi@marquette.edu

^[a]Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53201-1881 USA,
www.marquette.edu/chem/Yi.shtml

Abstract

The cationic ruthenium hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ has been found to be an effective catalyst for the oxidative C–H coupling reaction of phenols with aldehydes to give 2-acylphenol compounds. The coupling of phenols with α,β -unsaturated aldehydes selectively gives the flavene derivatives. The catalytic method mediates direct oxidative C–H coupling of phenol and aldehyde substrates without using any metal oxidants or forming wasteful byproducts.

Keywords

acylation; phenol; aldehyde; ruthenium; flavene

2-Acylphenols are a common core structure present in many biologically active natural products and pharmaceutical agents.^[1] Traditionally, Friedel-Crafts type of acylation reactions have been used to form acylated phenol compounds,^[2] but these methods have been found to be problematic in controlling product regioselectivity, tolerating common functional groups as well as in forming wasteful byproducts. Pd-catalyzed arene carbonylative coupling methods have greatly advanced synthetic potency for forming acyl-substituted arene compounds.^[3] However, these catalytic methods typically require prefunctionalization of substrates, which lead to the formation of salt byproducts. More recently, transition metal catalyzed C–H coupling methods have emerged as step-efficient, environmentally compatible ways to form arylketone compounds.^[4–8] Chelate assisted oxidative C–H acylation methods have been shown to be particularly effective in promoting regioselective introduction of acyl groups to indoles, benzamides and other functionalized arene compounds.^[5] The intramolecular catalytic C–H coupling methods,^[6] catalytic oxidative bond cleavage reactions,^[7] multicomponent coupling reactions of arenes with CO/olefins,^[8] and arene hydroxylation methods^[9] have also been successfully applied to form 2-acylarene products. While these catalytic C–H coupling methods directly install acyl group to arene substrates, the methods are mostly limited to aromatic aldehydes and often

Correspondence to: Chae S. Yi, chae.yi@marquette.edu.

Supporting information for this article is given via a link at the end of the document.

require stoichiometric metal oxidants. A broadly applicable oxidative C–H acylation method on phenol substrates is desired to enhance its synthetic efficacy toward the synthesis of bioactive acyl-substituted phenol compounds.

We recently discovered that a well-defined cationic ruthenium hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) is a highly effective catalyst precursor for a number of dehydrative C–H coupling reactions of phenols with alcohols to form 2-alkylphenol and benzofuran products.^[10] In light of the recent reports on the coupling reactions of alcohols,^[11] one of the key mechanistic questions concerns with whether the alcohol substrate undergoes dehydrogenation to form aldehyde prior to the dehydrative coupling reactions. We have been probing this possibility by exploring the reactivity of phenols toward aldehydes. Here, we report a highly regioselective oxidative C–H coupling of phenols with aldehydes to form 2-acylphenol and flavene products. The catalytic method mediates direct C–H activation of both phenol and aldehyde substrates without using any metal oxidants or resorting to prefunctionalization of phenol substrates.

(1)

Initially, we have chosen the coupling reaction of 3-methoxyphenol with benzaldehyde to probe the selectivity between the acylation vs alkylation products. The treatment of 3-methoxyphenol with benzaldehyde and the catalyst **1** (3 mol %) under the previously reported dehydrative coupling reaction conditions led to the formation of a 1:1 mixture of the acylated phenol product **2a** along with the alkylated product, but with only ~20% of the combined yield (eq 1).^[10] Suspecting that the aldehyde substrate might have been reduced to benzyl alcohol in leading to the alkylation product, we screened additive effects to optimize for the acylation product **2a**. Among screened additives and selected ruthenium catalysts, the complex **1** with base additives, K_2CO_3 and PPh_3 , was found to be the most effective in promoting the acylation product **2a** (Table S1, Supporting Information (SI)).

We explored the scope of the coupling reaction by using the optimized catalytic system (Table 1). Both aliphatic and aryl-substituted aldehydes readily reacted with 3-methoxyphenol to form the 2-acylphenol products **2** (entries 1–9). For the coupling of 3,5-dimethoxyphenol, electron-deficient benzaldehydes gave significantly higher yields than the ones with electron-releasing group (entries 10–18). The coupling of 1-naphthol with both aliphatic and aryl-substituted aldehydes gave the 2-acylated products **2s–2x** (entries 19–24), while the analogous coupling of 2-naphthol selectively yielded 1-acylnaphthol products **2y** and **2z** (entries 25, 26). Although the crude mixture typically contained a small amount of the alkylation product as well as unidentified oligomeric side products (5–10% combined), analytically pure acylated products were readily isolated after column chromatography on silica gel. In most cases, two equivalents of aldehyde is required for the optimum yield of coupling products, as the second equivalent of aldehyde is acting as an hydrogen

acceptor.^[12] The catalytic method achieves regioselective acylation of phenol substrates without using any stoichiometric metal oxidants or reactive reagents.

Flavonoids, a common group of polyphenol compounds in fruits and vegetables, have been shown to exhibit a wide range of pharmacological effects including anti-inflammatory, anti-aging and anticancer activities.^[13] To extend synthetic utility of the catalytic method, we next surveyed the coupling reaction of phenol substrates with α,β -unsaturated aldehydes to form flavonoid derivatives (Table 2). The coupling reaction of 3-methoxyphenol with both aliphatic and aryl-substituted enals smoothly occurred to give the substituted flavene derivatives (entries 1–6). A substantially higher product yield was obtained from the coupling of 3,5-dimethoxyphenol substrate with disubstituted enals (entries 7–12). The coupling with β -phenylcinnamaldehyde afforded the 2,2-disubstituted flavene product **3m** (entry 13). The analogous treatment of 1-naphthol and 9-phenanthrol with enals gave the corresponding polycyclic enol ether products **3n–3t** (entries 14–20). The formation of these flavene products **3** can be readily rationalized by *ortho*-C–H acylation followed by conjugate addition and dehydrative annulation sequences. The structure of 2-acylphenol and flavene products **2** and **3** was completely established by standard spectroscopic methods. The solid-state structures of **2v** and **3t** were also determined by X-ray crystallography (Figures S3 and S4, SI). Recently, a number of intermolecular and intramolecular coupling and annulation catalytic methods have been reported to form flavene derivatives, but these typically require prefunctionalization of substrates and multiple reaction steps.^[14]

The chemoselectivity of the coupling method has been explored by using bioactive phenol substrates (Scheme 1). For example, estrone reacted smoothly with both aliphatic and aryl-substituted aldehydes, 4-chlorobenzaldehyde and cyclohexanecarboxaldehyde, to give the 1:2 coupling products **4a** and **4b**, respectively. In this case, both arene C–H acylation and aldol-type couplings were occurred on the estrone substrate. Several attempts to form 1:1 coupling products were unsuccessful, as mixtures of both C–H acylation and aldol-type coupling products were resulted from using less than 1.5 equiv of aldehyde substrate. The structure of **4b**, as established by X-ray crystallography, clearly showed the (*E*)-enone configuration (Figure S5, SI).

We conducted the following preliminary experiments to gather mechanistic features. First, we examined the reaction of a phenol with a deuterium-labeled aldehyde to probe the possible H/D exchange pattern on both the phenol substrate and the products. The treatment of 3,5-dimethoxyphenol (0.5 mmol) with PhCDO (> 95% D, 1.0 mmol) in the presence of **1** (5 mol %), PPh₃ (20 mol %), and K₂CO₃ (30 mol %) in chlorobenzene (2 mL) was heated at 110 °C for 12 h, which led to 86 % conversion as analyzed by both GC-MS and NMR (eq 2). The ¹H and ²H NMR analysis showed exclusive deuterium incorporation on the benzyl position (83% D) of the isolated benzyl alcohol byproduct, but no deuterium incorporation was observed on either the starting material or the product **2j** (Figure S1, SI). The presence of mostly intact deuterium on α -CH₂ of benzyl alcohol byproduct suggests that the aldehyde substrate serves as both the hydrogen acceptor and the reagent for the coupling product.

(2)

To discern rate-limiting step of the coupling reaction, we next measured deuterium isotope effect of aldehyde substrate. Thus, the reaction rate of 3,5-dimethoxyphenol with PhCHO and PhCDO at 110 °C was measured separately (eq 3). The k_{obs} for each substrates was obtained from the first order plots of the formation of **2j**, which led to a normal deuterium isotope effect of $k_{\text{H}}/k_{\text{D}} = 3.3 \pm 0.3$ (Figure S2, SI). The observation of a relatively high normal deuterium isotope effect is consistent with the rate-limiting aldehyde C–H activation step.

(3)

To probe electronic influence on the aldehyde substrate, we constructed a Hammett plot by comparing the rate of a series of 3,5-dimethoxyphenol with *para*-substituted benzaldehydes $p\text{-X-C}_6\text{H}_4\text{CHO}$ ($\text{X} = \text{CH}_3, \text{H}, \text{F}, \text{Cl}, \text{CF}_3$). A linear correlation from the relative rate vs Hammett σ_{p} led to a positive ρ value of $+0.69 \pm 0.05$ (Figure 1). A strong promotional effect by the electron-withdrawing group suggests a substantial cationic character build-up on the carbonyl carbon in the transition state, which may be facilitated by the formation of Ru-acyl species. Similar Hammett ρ values have been observed in the catalytic coupling reactions of benzaldehyde and related arenes.^[15]

On the basis of these results, we compile a plausible mechanistic repertoire for the oxidative C–H acylation reaction (Scheme 2). We propose that the initial displacement of benzene ligand with phenol substrate and deprotonation of Ru–H and would generate a catalytically active neutral Ru-arene species **5**. In support of this notion, we previously observed a facile arene exchange reaction of **1** at room temperature.^[16] The observed H/D exchange pattern on both the coupling product as well as the recovered benzyl alcohol byproduct suggests a facile *ortho*-C–H activation of the phenol substrate to form a metallated species **6**. Hydrogenation of the first equivalent of aldehyde, coupled with the C–H activation of second aldehyde substrate, can be envisioned to rationalize the formation of the Ru-acyl intermediate **7**. Both the deuterium isotope effect and Hammett studies signify that the aldehyde C–H activation is the turnover limiting step of the catalytic cycle. The subsequent reductive elimination of the coupling product **2** and the binding of another phenol substrate would complete the catalytic cycle.

In a concluding remark, we successfully devised an *ortho*-selective C–H acylation protocol for phenol substrates. The Ru catalytic system expedites the direct oxidative coupling of simple phenol and aldehyde substrates to give 2-acylphenol and flavene products without using any external oxidants or resorting to multistep synthetic manipulations. Efforts to utilize the catalytic coupling method to synthesize bioactive flavene molecules are currently underway in our laboratory.

Experimental Section

General Procedure for the C–H Acylation of Phenol with Aldehyde

In a glove box, phenol (0.5 mmol), aldehyde (1.0 mmol), K₂CO₃ (30 mol %), PPh₃ (20 mol %) and complex **1** (14 mg, 5 mol %) were dissolved in chlorobenzene (2 mL) in a 25 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar. The tube was brought out of the glove box, and was stirred in an oil bath set at 110 °C for 8–16 h. The reaction tube was taken out of the oil bath, and was cooled to room temperature. After the tube was open to air, the solution was filtered through a short silica gel column by eluting with CH₂Cl₂ (10 mL), and the filtrate was analyzed by GC-MS. Analytically pure product was isolated by a simple column chromatography on silica gel (280–400 mesh, hexanes/EtOAc). The product was completely characterized by NMR and GC-MS spectroscopic methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support from the US National Science Foundation (CHE-1358439) and National Institute of Health General Medical Sciences (R15 GM109273) is gratefully acknowledged. The authors thank Dr. Sergey Lindeman for the X-ray crystal structure determination of **2v**, **3t** and **4b**.

References

1. a) Rappoport, Z. *The Chemistry of Phenols*. Wiley-VCH; Weinheim: 2003. b) Charest MG, Lerner CD, Brubaker JD, Siegel DR, Myers AG. *Science*. 2005; 308:395. [PubMed: 15831754] c) Gonzalez-Bello C, Castedo L. *Sci Synth*. 2007; 31a:319.
2. a) Gore PH. *Chem Rev*. 1955; 55:229. b) Olah, GA. *Friedel-Crafts Chemistry*. Wiley; New York: 1973.
3. a) Suzuki A. *Acc Chem Res*. 1982; 15:178. b) Miyaura N, Suzuki A. *Chem Rev*. 1995; 95:2457.
4. Recent reviews: Lyons TW, Sanford MS. *Chem Rev*. 2010; 110:1147. [PubMed: 20078038] Yeung CS, Dong VM. *Chem Rev*. 2011; 111:1215. [PubMed: 21391561] Arockiam PB, Bruneau C, Dixneuf PH. *Chem Rev*. 2012; 112:5879. [PubMed: 22934619] Thirunavukkarasu VS, Kozhushkov SI, Ackermann L. *Chem Commun*. 2014; 50:29.
5. a) Jia X, Zhang S, Wang W, Luo F, Cheng J. *Org Lett*. 2009; 11:3120. [PubMed: 19552400] b) Chan CW, Zhou Z, Chan ASC, Yu WY. *Org Lett*. 2010; 12:3926. [PubMed: 20704334] c) Li M, Ge H. *Org Lett*. 2010; 12:3464. [PubMed: 20670012] d) Baslé O, Bidange J, Shuai Q, Li CJ. *Adv Synth Catal*. 2010; 352:1145. e) Li C, Wang L, Li P, Zhou W. *Chem Eur J*. 2011; 17:10208. [PubMed: 21809404] f) Park J, Park E, Kim A, Lee Y, Chi K-W, Kwak JH, Jung YH, Kim IS. *Org Lett*. 2011; 13:4390. [PubMed: 21793534] g) Thirunavukkarasu VS, Donati M, Ackermann L. *Org Lett*. 2012; 14:3416. [PubMed: 22691029] h) Sharma S, Park J, Park E, Kim A, Kim M, Kwak JH, Jung YH, Kim IS. *Adv Synth Catal*. 2013; 355:332. i) Li H, Li P, Wang L. *Org Lett*. 2013; 15:620.

- [PubMed: 23343496] j) Zhang Q, Li C, Yang F, Li J, Wu Y. *Tetrahedron*. 2013; 69:320.k) Wang Z, Tian Q, Yu X, Kuang C. *Adv Synth Catal*. 2014; 356:961.l) Han S, Sharma S, Park J, Kim M, Shin Y, Mishra NK, Bae JJ, Kwak JH, Jung YH, Kim IS. *J Org Chem*. 2014; 79:275. [PubMed: 24320114]
6. a) Tang BX, Song RJ, Wu CY, Liu Y, Zhou MB, Wei WT, Deng GB, Yin DL, Li JH. *J Am Chem Soc*. 2010; 132:8900. [PubMed: 20540581] b) Álvarez-Bercedo P, Flores-Gaspar A, Correa A, Martin R. *J Am Chem Soc*. 2010; 132:466. [PubMed: 20038097]
7. a) Li CJ. *Acc Chem Res*. 2009; 42:335. [PubMed: 19220064] b) Rao H, Li CJ. *Angew Chem Int Ed*. 2011; 50:8936.c) Yao J, Feng R, Wu Z, Liu Z, Zhang Y. *Adv Synth Catal*. 2013; 355:1517.
8. a) Kakiuchi F, Murai S. *Acc Chem Res*. 2002; 35:826. [PubMed: 12379135] b) Kakiuchi F, Chatani N. *Adv Synth Catal*. 2003; 345:1077.
9. a) Shan G, Yang X, Ma L, Rao Y. *Angew Chem Int Ed*. 2012; 51:13070.b) Mo F, Trzepakowski LJ, Dong G. *Angew Chem Int Ed*. 2012; 51:13075.c) Thirunavukkarasu VS, Ackermann L. *Org Lett*. 2012; 14:6206. [PubMed: 23210732] d) Choy PY, Kwong FY. *Org Lett*. 2013; 15:270. [PubMed: 23301995] e) Yang F, Rauch K, Kettelhoit K, Ackermann L. *Angew Chem Int Ed*. 2014; 53:11285.
10. Lee DH, Kwon KH, Yi CS. *J Am Chem Soc*. 2012; 134:7325. [PubMed: 22494241]
11. a) Gunanathan C, Milstein D. *Acc Chem Res*. 2011; 44:588. [PubMed: 21739968] b) Obora Y. *ACS Catal*. 2014; 4:3972.
12. Using more than two equivalents of aldehyde did not improve the product yields, as excess aldehydes were found to form homocoupling products.
13. a) Middleton E Jr, Kandaswami C, Theoharides TC. *Pharm Rev*. 2000; 52:673. [PubMed: 11121513] b) Boots AW, Haenen GRMM, Bast A. *Eur J Pharm*. 2008; 585:325.
14. a) Pastine SJ, Youn SW, Sames D. *Org Lett*. 2003; 5:1055. [PubMed: 12659572] b) van Otterlo WAL, Ngidi EL, Kuzvidza S, Morgans GL, Moleele SS, de Koning CB. *Tetrahedron*. 2005; 61:9996.c) Aponick A, Biannic B, Jong MR. *Chem Commun*. 2010; 46:6849.d) Madabhushi S, Jillella R, Godala KR, Mallu KKR, Beeram CR, Chinthala N. *Tetrahedron Lett*. 2012; 53:5275.
15. Selected recent examples: Fristrup P, Kreis M, Palmelund A, Norrby PO, Madsen R. *J Am Chem Soc*. 2008; 130:5206. [PubMed: 18303836] Koren-Selfridge L, Londino HN, Vellucci JK, Simmons BJ, Casey CP, Clark TB. *Organometallics*. 2009; 28:2085.Sigman MS, Werner EW. *Acc Chem Res*. 2012; 45:874. [PubMed: 22111756]
16. Kwon KH, Lee DW, Yi CS. *Organometallics*. 2010; 29:5748. [PubMed: 21344062]

Figure 1. Hammett Plot from the Reaction of 3,5-Dimethoxyphenol with p -X-C₆H₄CHO (X = CH₃, H, F, Cl, CF₃).

Scheme 1.

Oxidative C–H Acylation and Aldol-Type Coupling of Estrone with Aldehydes.

Scheme 2.
Mechanistic Hypothesis for the C–H Oxidative Acylation of Phenol with an Aldehyde.

Table 1

Oxidative C–H Acylation of Phenols with Aldehydes.^[a]

entry	phenol	aldehyde	product(s)	time (h)	yield (%)
1				12	47
2		X=H	2a	12	43
3		X=4-Me	2b	12	53
4		X=4-F	2c	12	58
		X=2-Br	2d	12

5		R = Et	2e	12	56
6		R = <i>n</i> -Pr	2f	12	44
7		R = <i>i</i> -Bu	2g	12	58
8		R = Cy	2h	12	50
9		R = CH(Me)Ph	2i	12	67

10		X = H	2j	16	65
11		X = Me	2k	16	51
12		X = F	2l	16	73
13		X = Cl	2m	16	70

entry	phenol	aldehyde	product(s)	time (h)	yield (%)
14		$X = CF_3$	2n	16	74
15			2o	8	74
16		$R = i\text{-Bu}$	2p	12	69
17		$R = Cy$	2q	12	71
18		$R = CH(Me)Ph$	2r	12	78
19		$X = H$	2s	8	48
20		$X = F$	2t	8	35
21		$R = Et$	2u	8	47
22		$R = Cy$	2v	8	40
23		$R = 3\text{-cyclohexenyl}$	2w	12	33
24		$R = CH(Me)Ph$	2x	12	61

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

entry	phenol	aldehyde	product(s)	time (h)	yield (%)
25		R=Ph	2y	20	35
26		R=Cy	2z	20	38

^[a] Reaction conditions: phenol (0.5 mmol), aldehyde (1.0 mmol), **1** (5 mol %), PPh₃ (20 mol %), K₂CO₃ (30 mol %), C₆H₅Cl (2–3 mL), 110 °C.

Table 2

Oxidative C–H Acylation and Dehydrative Annulation of Phenols with α,β -Unsaturated Aldehydes.^[a]

entry	phenol	aldehyde	product	temp (°C)	time (h)	yield (%)
1				110	24	37
2		$R_1 = H$ $R_2 = H$		130	16	23
3		$R_1 = Me$ $R_2 = H$		130	16	43
4		$R_1 = n\text{-Hexyl}$ $R_2 = H$		130	16	63
5		$R_1 = H$ $R_2 = Ph$		130	16	40
6				130	16	53
7		$R_1 = H$ $R_2 = n\text{-Pr}$		120	16	54
8		$R_1 = Me$ $R_2 = Et$		120	16	47
9		$R_1 = H$ $R_2 = Ph$		120	16	52
10		$R_1 = H$ $R_2 = 4\text{-F-Ph}$		120	16	55

entry	phenol	aldehyde	product	temp (°C)	time (h)	yield (%)
11		R ₁ = Me R ₂ = Ph		120	16	72
12		R ₁ = <i>n</i> -Hexyl R ₂ = Ph		120	16	88
13				130	16	63
14				100	20	40
15		R ₁ = H R ₂ = <i>n</i> -Pr		130	12	46
16		R ₁ = Me R ₂ = Ph		130	12	42
17		R ₁ = <i>n</i> -Hexyl R ₂ = Ph		130	12	59
18		R ₁ = H R ₂ = H R ₃ = <i>n</i> -Pr		120	16	71
19		R ₁ = Me R ₂ = H R ₃ = Ph		120	16	60
20		R ₁ = H R ₂ = Ph R ₃ = Ph		120	16	56

[a] Reaction conditions: phenol (0.5 mmol), aldehyde (1.0 mmol), **1** (5 mol %), PPh₃ (20 mol %), C₆H₅Cl (2–3 mL).