ORGANIC LETTERS

2012
Vol. 14, No. 3
902–905

Rhodium-Catalyzed Xanthone Formation from 2-Aryloxybenzaldehydes via Cross-Dehydrogenative Coupling (CDC)

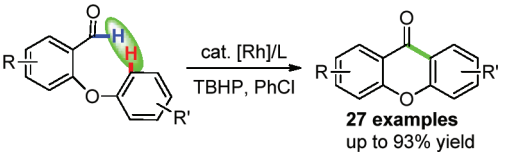
Ping Wang,[†,‡] Honghua Rao,[†] Ruimao Hua,[‡] and Chao-Jun Li*[,†]

Department of Chemistry, McGill University, Montreal, QC H3A 2K6, Canada, and Department of Chemistry, Tsinghua University, Beijing 100084, China

cj.li@mcgill.ca

Received December 22, 2011

ABSTRACT



A concise and straightforward strategy to construct a xanthone skeleton via an intramolecular cross-dehydrogenative coupling (CDC) of 2-aryloxybenzaldehydes has been developed. The reaction proceeded smoothly without any need of preactivation of the aldehyde group. It can tolerate various functional groups and provides an applicable protocol to construct a wide range of xanthone derivatives.

The xanthone substructure is of great significance in natural products such as mangiferin and psorospermin (Figure 1) due to its excellent biological and pharmacological activities.[1a,b] Thus, construction of such substructures has always been synthetically attractive.[1c−g] Various approaches to the xanthone skeleton from a range of functionalized diaryl ethers via varied mechanisms have been developed, most frequently, via the Friedel−Crafts reactions. In the early days, Jackson used aluminum chloride and oxalyl chloride to obtain xanthones from diaryl ethers in methylene chloride at room temperature.[2] Later, Snieckus reported an LDA-mediated conversion from 2-carbamoyl diaryl ethers to xanthone derivatives. This was considered to be an anionic Friedel−Crafts process driven by the complex induced proximity effect.[3] Subsequently, Frahm presented a series of substituted xanthones synthesized from 2-aryloxybenzoic acids in the presence of PPA.[4] Recently, Lu resorted to copper(II)-catalyzed aza-Friedel−Crafts reaction of *o*-phenoxyl *N*-tosylbenzaldimine to construct nonsubstituted xanthone.[5] On the other hand, Larock used arylated imino group at the *ortho* position of the aryl ether as the functional group to be activated.

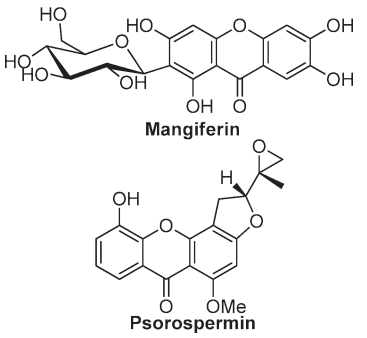


Figure 1. Xanthone structure in natural products.

(1) (a) Daud, N. H.; Aung, C. S.; Hewavitharana, A. K.; Wilkinson, A. S.; Pierson, J.; Roberts-Thomson, S. J.; Shaw, P. N.; Monteith, G. R.; Gidley, M. J.; Parat, M. *J. Agric. Food Chem.* **2010**, *58*, 5181. (b) Kupchan, S. M.; Streelman, D. R.; Sneden, A. T. *J. Nat. Prod.* **1980**, *43*, 296. (c) Roberts, J. C. *Chem. Rev.* **1961**, *61*, 591. (d) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522. (e) Kenji, M.; Yukihiro, A.; Hong, Y.; Kenji, O.; Tetsuro, I.; Toshiyuki, T.; Emi, K.; Munekazu, I.; Yoshinori, N. *Bioorg. Med. Chem.* **2004**, *12*, 5799. (f) Pedro, M.; Cerqueira, F.; Sousa, M. E.; Nascimento, M. S. J.; Pinto, M. *Bioorg. Med. Chem.* **2002**, *10*, 3725. (g) Peres, V.; Nagem, T. J.; Faustino de Oliveira, F. *Phytochemistry* **2000**, *55*, 683.

(2) Jackson, W.; Boyd, R.; Froelich, L.; Gapinski, D.; Mallett, B.; Sawyer, J. *J. Med. Chem.* **1993**, *36*, 1726.

(3) Familoni, O.; Ionica, I.; Bower, J.; Snieckus., V. *Synlett* **1997**, 1081.

(4) Pickert, M.; Frahm, A. W. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 177.

(5) Yu, X.; Lu, X. *Tetrahedron Lett.* **2011**, *52*, 2076.

10.1021/ol203381q
Published on Web 01/24/2012

Through aryl to imidoyl palladium migration, the imidoyl C−H bonds were activated, and xanthones were formed subsequently.[6] In addition, Liebeskind achieved the xanthone skeleton by a cascade of electrocyclization reactions of cyclobutenedione derivatives via the benzannulation intermediate, providing a complementary xanthone syntheses.[7]

Recently, we and others have successfully realized various C−C bond formations through the direct reaction of two C−H bonds, which was termed cross-dehydrogenative coupling (CDC).[8] Among them, cross-dehydrogenative-coupling between aromatic C−H bonds and arylated aldehyde C−H bonds has offered a powerful tool to produce diaryl ketones.[9] Recently, Li's group found that 2-aryloxybenzaldehydes can undergo an unprecedented rearrangement by cleavage of both aryloxy C−O bonds and aldehyde C−H bonds to form 2-hydroxy-benzophenones in the presence of $[\{RhCl(CO)_2\}_2]$.[10] Further investigations on the decarbonylation of 2-aryloxybenzaldehydes to form dibenzo[*b*,*f*]furans were conducted, in which xanthones were isolated in a considerable yield. Herein, we present the first example to construct xanthone skeleton via the CDC process from 2-aryloxybenzaldehydes directly without preactivation of the aldehyde group. In addition, the excellent tolerance of diverse catalytically reactive substituent groups makes the reaction a fairly general synthesis protocol to xanthones, which will complement the Friedel−Crafts approaches (Scheme 1).

Scheme 1. One-Step Synthesis of Xanthones from Diaryl Ethers

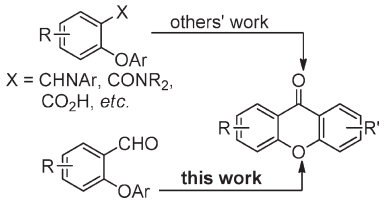
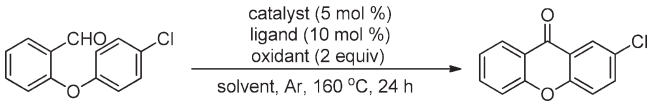


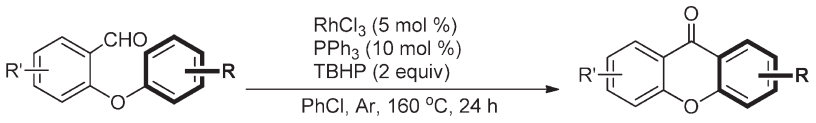
Table 1. Optimization of the CDC Reaction of 2-(*p*-Chlorophenoxy)benzaldehyde[a]

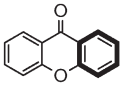
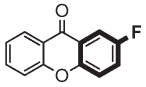
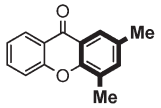
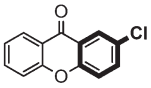
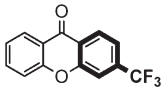
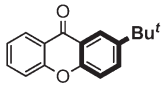
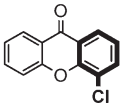
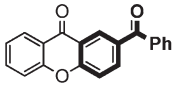
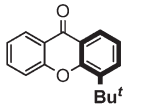
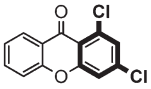
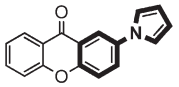
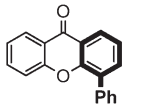
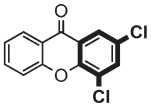
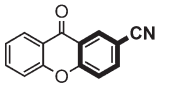
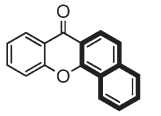
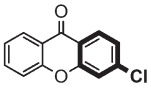
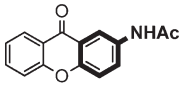
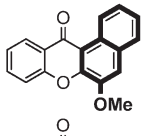
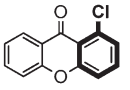
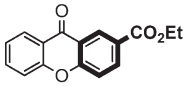
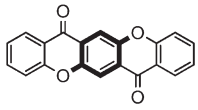
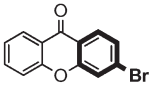
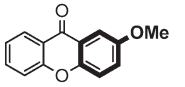
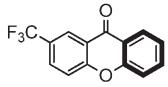
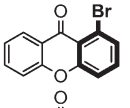
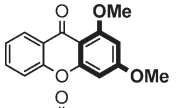
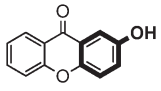
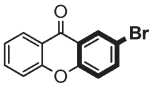
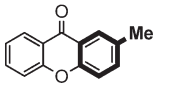


entry	catalyst	ligand	oxidant	solvent	yield (%)[b]
1	$Rh(CO)_2(acac)$		TBHP (in decane)	PhCl	12
2	$[RhCl(COD)]_2$		TBHP (in decane)	PhCl	16
3	$RhCl(CO)(PPh_3)_2$		TBHP (in decane)	PhCl	7
4	$[Rh(COD)_2]BF_4$		TBHP (in decane)	PhCl	29
5	$RhCl(PPh_3)_3$		TBHP (in decane)	PhCl	28
6	$Rh_2(OAc)_4$		TBHP (in decane)	PhCl	10
7	$[Cp^*RhCl_2]_2$		TBHP (in decane)	PhCl	15
8	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$		TBHP (in decane)	PhCl	30
9	$RhCl_3$		TBHP (in decane)	PhCl	49
10	**$RhCl_3$**	**PPh_3**	**TBHP (in decane)**	**PhCl**	**54 (49)**
11	$RhCl_3$	$P(2,4,6\text{-}Me_3C_6H_2)_3$	TBHP (in decane)	PhCl	45
12	$RhCl_3$	$P(2\text{-furyl})_3$	TBHP (in decane)	PhCl	41
13	$RhCl_3$	dppe	TBHP (in decane)	PhCl	50
14	$RhCl_3$	dppp	TBHP (in decane)	PhCl	45
15	$RhCl_3$	xyl-BINAP	TBHP (in decane)	PhCl	46
16	$RhCl_3$	PPh_3	TBHP (in decane)	toluene	50
17	$RhCl_3$	PPh_3	TBHP (in decane)	xylene	38
18	$RhCl_3$	PPh_3	TBHP (in decane)	CH_3CN	40
19	$RhCl_3$	PPh_3	TBHP (in decane)	*i*-propanol	13
20	$RhCl_3$	PPh_3	TBHP (in decane)	dioxane	25
21	$RhCl_3$	PPh_3	TBHP (in decane)	DCE	45
22	$RhCl_3$	PPh_3	TBHP (in decane)	Py	39
23	$RhCl_3$	PPh_3	TBP	PhCl	20
24	$RhCl_3$	PPh_3	TBPB	PhCl	24
25	$RhCl_3$	PPh_3	DDQ	PhCl	NR
26[c]	$RhCl_3$	PPh_3	TBHP (in decane)	PhCl	50
27[d]	$RhCl_3$	PPh_3	TBHP (in decane)	PhCl	46
28[e]	$RhCl_3$	PPh_3	TBHP (in decane)	PhCl	48

[a] Reactions were carried out with 2-(*p*-chlorophenoxy)benzaldehyde (0.2 mmol), catalyst (5 mol %), ligand (10 mol %), oxidant (2 equiv) in solvent (0.4 mL) at 160 °C under argon for 24 h. [b] Yield determined by ^1H NMR spectroscopy using mesitylene as the internal standard; the number in parentheses is isolated yield. [c] The reaction was carried out at 120 °C. [d] The reaction was run for 16 h. [e] The reaction was run for 36 h.

Table 2. Scope of the CDC Reaction of 2-Aryloxybenzaldehydes to Xanthones[a]



entry	product		yield (%)[b]	entry	product		yield (%)[b]	entry	product		yield (%)[b]
1		**2a**	93	9		**2i**	77	19		**2s**	63
2		**2b**	49	10		**2j**	50	20		**2t**	91
3		**2c**	42	11		**2k**	53	21		**2u**	36
4		**2d**	39	12		**2l**	80	22		**2v**	53
5		**2e**	25	13		**2m**	23	23		**2w**	36
6		**2f**$_a$	49 (2:1)	14		**2n**	46	24		**2x**	39
		**2f**$_b$		15		**2o**	32	25		**2y**	43
7		**2g**$_a$	66 (1:1)	16		**2p**	82	26		**2z**	78
		**2g**$_b$		17		**2q**	81	27		**2a'**	34
8		**2h**	70	18		**2r**	80				

[a] Reactions were carried out with 2-aryloxybenzaldehyde (0.2 mmol), $RhCl_3$ (5 mol %), PPh_3 (10 mol %), TBHP (2 equiv) in PhCl (0.4 mL) at 160 °C under argon for 24 h. [b] Isolated yield.

To start, we chose 2-(*p*-chlorophenoxy)benzaldehyde as the model substrate to obtain the optimal reaction conditions. On the basis of our initial observed xanthone product, the catalytic activities of different rhodium catalysts (5 mol %) were examined by carrying out the reaction at 160 °C for 24 h with 2 equiv of *tert*-butyl hydroperoxide (TBHP) as the oxidant and chlorobenzene as the solvent. As is shown in Table 1, $RhCl_3$ is much more efficient than other rhodium catalysts tested, giving a yield of 49% in contrast to others (30%) (entries 1−9, Table 1). The presence of phosphine ligands affected the reaction to some extent. Among them, PPh_3 increased the yield to 54%, while others exerted almost no effect or even worked

(6) Zhao, J.; Yue, D.; Campo, M.; Larock, R. *J. Am. Chem. Soc.* **2007**, *129*, 5288.

(7) Sun, L.; Liebeskind., L. *Tetrahedron Lett.* **1997**, *38*, 3663.

(8) (a) Li, Z.; Li, C. -J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Li, C. -J. *Acc. Chem. Res.* **2009**, *42*, 335. (d) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 8928. (e) Yoo, W. -J.; Li, C. -J. *Top. Curr. Chem.* **2010**, *292*, 281.

(9) (a) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Liu, Y.; Zhou, M.-B.; Wei, W.-T.; Deng, G.-B.; Yin, D.-L.; Li, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8900. (b) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (c) Chan, C. -W.; Zhou, Z.; Chan, A. S. C.; Yu, W. -Y. *Org. Lett.* **2010**, *12*, 3926. (d) Basle, O.; Bidange, J.; Shuai, Q.; Li, C. -J. *Adv. Synth. Catal.* **2010**, *352*, 1145.

(10) Rao, H. -H.; Li, C. -J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8936.

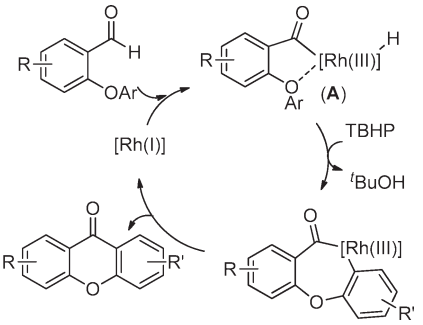
negatively (entries 10–15, Table 1). The screening of solvents demonstrated that chlorobenzene was superior to other solvents such as toluene and xylene, protic solvent *i*-propanol, ether solvent dioxane, basic solvent pyridine, and so on (entries 16–22, Table 1). As to the oxidant, TBHP provided the best yield (entry 23–25, Table 1). Lowering the reaction temperature led to a relatively lower yield (entry 26, Table 1) and so did a shorter reaction time (entry 27, Table 1). However, a prolonged reaction time did not increase the yield either (entry 28, Table 1). Consequently, the reaction was carried out with 5 mol % $RhCl_3$ as the catalyst, 10 mol % PPh_3 as the ligand, and 2 equiv of TBHP as the oxidant in chlorobenzene at 160 °C for 24 h.

With the optimized conditions in hand, the scope of the reaction was investigated. The results are listed in Table 2. To our delight, the reaction can serve as a really general protocol to the syntheses of various substituted xanthones, affording moderate to excellent yields bearing both electron-donating and electron-withdrawing substituents. More importantly, this strategy showed an excellent tolerance to diverse catalytically reactive substituent groups such as aryl halides, amide, ketone, ester, and a cyano group (entries 2–17, Table 2). Generally speaking, the aryloxy parts with electron-donating groups were relatively more reactive than those with electron-withdrawing ones, and hence gave relatively higher yields. However, substituents at the *ortho* position of the aryloxy group reduced the yield, possibly due to steric effect (entries 21–24, Table 2). If the substituent was at the *meta* position, xanthones were obtained as isomers in some cases. For example, when 2-(*m*-bromophenoxy) benzaldehyde was used, we obtained a 1:1 mixture of 3-bromo-9*H*-xanthen-9-one and 1-bromo-9*H*-xanthen-9-one (entry 7, Table 2). However, for 2-(*m*-chlorophenoxy) benzaldehyde, the ratio of 3-chloro-9*H*-xanthen-9-one to 1-chloro-9*H*-xanthen-9-one became 2:1 (entry 6, Table 2). When it was switched to 2-(*m*-trifluoromethylphenoxy) benzaldehyde, only 3-trifluoromethyl-9*H*-xanthen-9-one was obtained (entry 10, Table 2). Such differences could be attributed to the distinction between the electron-withdrawing capacity of these three substituents.

Disubstituted ethers could also proceed via the CDC reaction under the optimized conditions, affording a structure with double xanthone skeletons (entry 25, Table 2). In addition, a free hydroxyl group could also be tolerated in this reaction (entry 27, Table 2).

A tentative mechanism for the reaction is proposed in Scheme 2. A sequence of an oxidative addition of the aldehyde C–H bond, an oxidative dehydrogenation, and finally a reductive elimination gave the desired product. In this process, the stability of the five-membered ring intermediate **A** has prevented decarbonylation, generating the sebsequent oxidative dehydrogenation product predominantly.

Scheme 2. Proposed Mechanism



In summary, we have developed a new way to construct xanthone skeletons from aldehydes directly. It does not require any preactivation of the aldehyde group. In addition, the reaction can tolerate diverse functional groups and can be applied to obtain a rather wide range of xanthone derivatives. In this sense, it is a useful complementary method for synthesizing xanthones.

Acknowledgment. We are grateful to the Canada Research Chair Foundation (to C.J.L.), the CFI, FQRNT Center for Green Chemistry and Catalysis, NSERC, and McGill University for support of our research. P.W. also thanks the China Scholarship Council for financial support.

Supporting Information Available. Typical experimental procedure and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.