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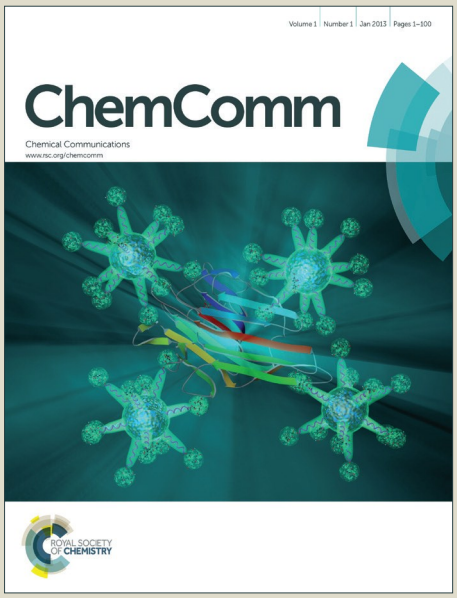

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Chemical Communication

EDGE ARTICLE

Acylation of Csp^2-H bond with acyl sources derived from alkynes: Rh-Cu Bimetallic Catalyzed C≡C bond cleavage †

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A Rh-Cu bimetallic catalyzed o-acylation of acyloxacetamide with alkynes has been described. This transformation provides a novel concise way to synthesize *ortho*-Acylphenols *using* functionalized alkynes as acylated reagent. Mchanistic study revealed the Rh-Cu relay process, in which O_2 plays a critical role for formation of the carbonyl compounds.

Introduction

Aryl ketones are common Skelton in many classes of biologically active compounds and natural products (figure 1).[1] Consequently, how to synthesize these products has drawn much attention, and various of methods have been developed for the preparation of aryl ketones. Traditional methods carried out to access these compounds by using activated substrates (Friedel-Crafts).[2] Recently, transition-metal-catalyzed C-H functional reaction is considered as a powerful strategy for the construction of these ketones.[3] In this regards, various directing group assisted Csp^2-H bond acylation with aldehydes,[4] alcohols[5], toluenes [6]or α-oxocarboxylic acid [7]as acyl surrogates for the synthesis of the aryl ketones were described. Despite these impressive advances, acylation of phenol within a single step is scarce except Wang group has been develop perfect work Copper-catalyzed ortho-acylation of phenols with aryl aldehydes [8]. so how to develop a novel, more efficiently acyl surrogate for the access to *ortho*-Acylphenols is still in urgent need.

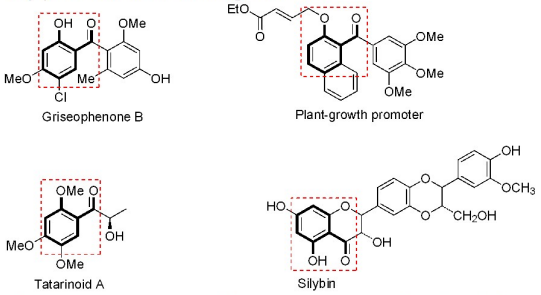
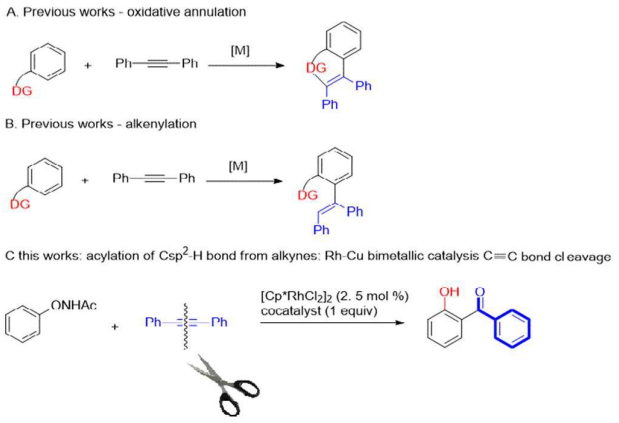


Figure 1. Natural and drug containing ortho-Acylphenols

Previous works demonstrated that transition-metal-catalyzed cross coupling reactions *via* directing-group-assisted with alkyne have been considered as powerful tools for variety cyclic compounds through (3+2),[9] (4+2),[10] (5+2) cycloaddition to products[11]. until now, the Csp^2-H acylation of arenes using novel acyl sources derived from the transition-metal-catalyzed cleavage of C≡C bonds remains unknown (Scheme 1c). Jiao's works have been indicated that alkenes can be efficiently oxidized and further promoted C=C bond cleavage for carbonylation.[12] Therefore, we assume alkynes can be converted to electron-rich olefins that may be oxidized under Jiao's catalyst system for the construction of the carbonyl compounds. Recently multiple function of alkynes have been achieved by the atom transfer C-H function strategy[13], for example, Lu's group developed a method of transformation from amide to multiple alkynes using Rh(III) as catalysts [14] subsequently Zhao and co-works have been reported that a several heterocyclic scaffolds was been given by base on the orthohydroxyphenyl-substituted enamides intermiedate by cocatalyst regulation [15]. Inspired by these transformations, we described a Rh-Cu catalyzed cascade reaction of alkynes with *N*-phenoxyacetamides to give *ortho*-Acylphenols under mild conditions.



Scheme 1 Acylation of Csp^2-H bond with acyl sources derived from alkynes: Rh-Cu Bimetallic Catalyzed C≡C bond cleavage

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[b] *† Footnotes relating to the title and/or authors should appear here.*
Electronic Supplementary Information (ESI) available: CCDC 1443747. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x

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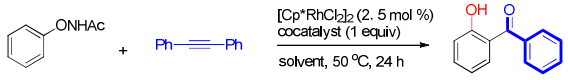
Results and discussion

Optimization studies

In preliminary experiments, *N*-phenoxyacetamide (**1a**) was treated with [{Cp*$RhCl_2$}$_2$] (2.5 mol%), NHPI (20 mol%)[11b], and alkyne (**2a**) in MeOH at 30 ˚C for 24 hours under air, however no desired product was observed (table 1, entry 1). Then a search for appropriate additives was pursued, previous investigations by Jiao demonstrated that Cu/O_2 catalyst system could be efficient for the cleavage of C=C, C≡C bonds of carbonyl derivatives. So we tried various cooper salts as additives for the reaction. Among of these salts, $Cu(OAc)_2$ could give a moderated yield of the desired product (54%, table 1, entry 7) while other Cu additives give poor yields (table 1, entry 2-6). Subsequently, various parameters were screened to improve the reaction efficiency (see Supporting Information (SI)). The results showed that the solvent (Table 1, entry 7-10) had great influence on the reaction yield and Methanol was proven to be the most suitable candidate for this transformation. When we investigated the effect of the reaction temperature on this transformation, we found that higher reaction temperatures (50 °C and 80 °C) could lead to the yield of **3a** 86% and 80% respectively (entry 12 and 13).

Table 1. Optimization of Reaction Conditions [a]



1a 2a 3a

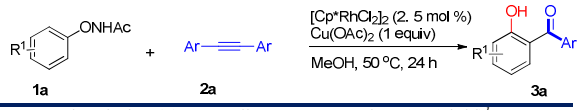
entry	catalysts	additives	solvent	yield (%)[b]
1	[Cp*$RhCl_2$]$_2$	NHPI	MeOH	0
2	[Cp*$RhCl_2$]$_2$	$CuCl_2$	MeOH	20
3	[Cp*$RhCl_2$]$_2$	$CuBr_2$	MeOH	32
4	[Cp*$RhCl_2$]$_2$	CuO	MeOH	18
5	[Cp*$RhCl_2$]$_2$	$Cu(CN)_2$	MeOH	12
6	[Cp*$RhCl_2$]$_2$	$CuSO_4$	MeOH	8
7	[Cp*$RhCl_2$]I_2	$Cu(OAc)_2$	MeOH	54
8	[Cp*$RhCl_2$]$_2$	$Cu(OAc)_2$	EtOH	45
9	[Cp*$RhCl_2$]$_2$	$Cu(OAc)_2$	i-PrOH	12
10	[Cp*$RhCl_2$]$_2$	$Cu(OAc)_2$	t-AmOH	Trace
12	[Cp*$RhCl_2$]$_2$	$Cu(OAc)_2$	MeOH	86[c]
13	[Cp*$RhCl_2$]$_2$	$Cu(OAc)_2$	MeOH	80[d]
14	[Cp*$RhCl_2$]$_2$		MeOH	0
15		$Cu(OAc)_2$	MeOH	0

[a] Unless otherwise noted, all the reactions were carried out using (**1a**) (0.10 mmol) and (**2a**) (0.15 mmol) with metal catalysts (2.5 mol %) in the presence of co-catalyst (1 equiv) in solvent (2.0 mL)at 30 ˚C for 24 h under air in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Isolated yield. [c] The reaction temperature is 50 °C. [d] The reaction temperature is 80 °C.

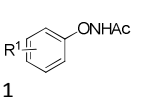
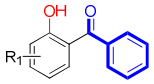
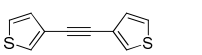
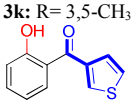
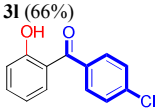
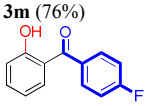
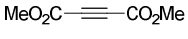
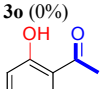
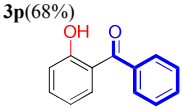
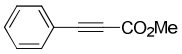
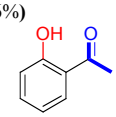
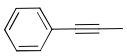
Substrate scope

With the optimized conditions in hand, we next investigated the substrate scope of this reaction with various internal alkynes and different substituted *N*-phenoxyacetamides. This transformation could tolerate various groups at the *para*-position such as Me, Ph, CF_3 and CO_2Me, affording the desired products **3b**, **3c**, **3h** and **3i** in moderate to good yields. Also, the halogen substituents were well tolerated under the optimized conditions to give products **3e**-**3g**. Generally, the electron-donating groups provide superior yields to electron-withdrawing groups. Furthermore, it is noteworthy that the *meta*-Chloro-substituted *N*-phenoxyacetamides (**1j**) gave the desired product with high regioselectivity and moderate yields. Whereas the *ortho*-substituted *N*-phenoxyacetamides (**1d**) gave poorer yield of product (**3d**) due to higher steric hindrance. Subsequently, variety of internal alkynes as acyl sources was also tested. It was found that not only a broad scope of symmetrical (e.g. aromatic heterocyle substituted interalkyne, 2-Butyne) but also unsymmetrically substituted internal alkynes could efficiently react with **1a** to give the corresponding products in moderate yields.

Table 2. Substrate scope [a]



1a 2a 3a

entry	ketoimine (**1**)	alkyne (**2**)	product (**3**) (yield)[b]
1			
	1	**2a**	**3**
	1a: R= H	**2a**	**3a**: R= H (85%)
	1b: R= *p*-Me	**2a**	**3b**: R= *p*-Me (88%)
	1c: R= *p*-Ph	**2a**	**3c**: R= *p*-Ph (80%)
	1d: R= *o*-Me	**2a**	**3d**: R= *o*-Me (44%)
	1e: R= *p*-Cl	**2a**	**3e**: R= *p*-Cl (78%)
	1f: R= *p*-Br	**2a**	**3f**: R= p-Br (78%)
	1g: R= *p*-F	**2a**	**3g**: R= *p*-F(59%)
	1h:R=*p*-CF_3	**2a**	**3h**:R=*p*-CF_3 (70%)
	1i: R=*p*-CO_2Me	**2a**	**3i**: R= *p*-CO_2Me (67%)
	1j: R= *m*-Cl	**2a**	**3j**: R= *m*-Cl (65%)
	1k: R= 3,5-CH_3	**2a**	**3k**: R= 3,5-CH_3 (76%)
2		**2b**	
	1a		**3l** (66%)
3		**2c**	
	1a		**3m** (76%)
4		**2d**	
	1a		**3n** (74%)
5		**2e**	
	1a		**3o** (0%)
6		**2f**	
	1a		**3p**(68%)
7		**2g**	
	1a		**3a**(56%)
8		**2h**	
	1a		**3p**(60%)

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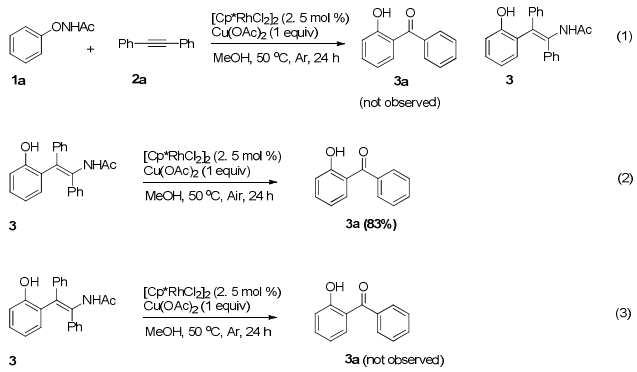
[a]All the reactions were carried out using (**1**) (0.10 mmol) and alkyne (**2**) (0.15 mmol) with $[Cp^*RhCl_2]_2$ (2.5 mol %) and co-catalyst (1equiv) in MeOH (2.0 mL) at 50 ˚C for 24 h under air in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Isolated yield.

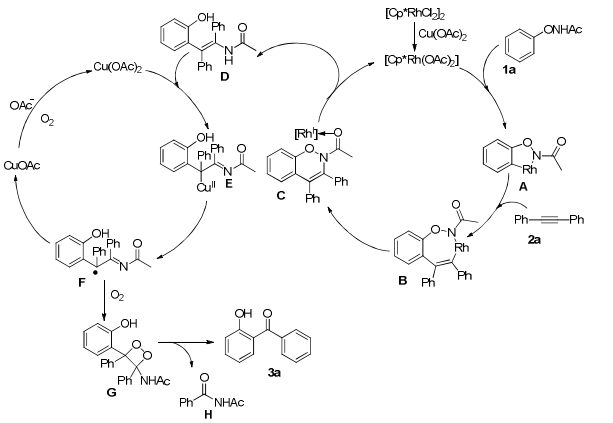
Mechanistic insights

To further investigate the reaction mechanism, several control experiments were carried out (scheme 4). At first, we ran the reaction in the presence of argon under our standard conditions (eq. 1.). No desired products were observed and by-product enamide **3** was isolated in 68% yield. We then treated the enaminde **3** in the presence of air and argon under our standard conditions respectively (eq. 2 and eq.3). Not surprisingly, no desired products was found when argon was involved in this transformation. Finally this result suggests that enamide **3** might be the intermediate of the reaction and the oxygen originated from air is crucial to the reaction.



Scheme 2 Preliminary Mechanism Studies

On the basis of the above result and previous studies,[16] a possible reaction mechanism has been proposed in Scheme 5. Presumably, the transformation starts with concerted-metalation-deprotonation step (CMD) to give the five-membered rhodacycle intermediate **A**, followed by alkyne coordination and insertion to afford the seven-membered intermediate **B**, which undergoes reductive elimination/oxidative addition to give intermediate **D**. Then the intermediate **D** was capped by the Cu/O_2 and provides the strained four-membered **G,** which finally undergoes the elimination of *N*-acetylbenzamide **H** leading to the desire products.



Scheme 3. Possible Mechanism for the Transformation

Conclusions

In summary, we have developed a facile and convenient method for the Rh(Ⅲ)-catalyzed acylation of Csp^2-H bond of *N*-phenoxyacetamide with alkyne under mild conditions using alkyne as a novelacyl source. The reaction exhibits a good tolerance for a broad range of functional groups and a variety of alkynes could be employed as acyl sources to afford *ortho*-acylphenols. Detailed mechanism studies on this method and more transformations using alkynes as acyl sources are being carried out in our laboratory.

Acknowledgements

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Notes and references

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Chemical Communication

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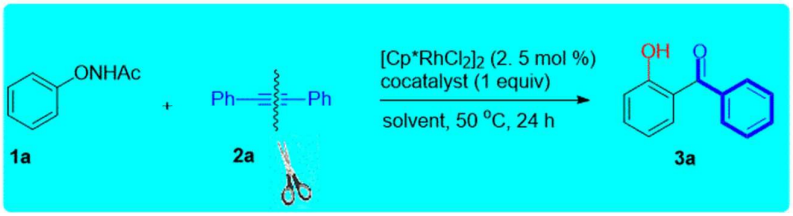

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Acylation of Csp^2-H bond with acyl sources derived from alkynes: Rh-Cu Bimetallic Catalyzed C≡C bond cleavage