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Original article

Rhodium catalyzed regioselective arene homologation of aryl urea via double C–H bond activation and migratory insertion of alkyne

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ABSTRACT

A convenient rhodium catalyzed oxidative arene homologation of aniline derivatives with symmetrical or unsymmetrical alkynes using $\text{Cu}(\text{OAc})_2$ as oxidant is described. Urea group is shown to be effective as a directing group for initial *ortho* C–H activation. Two migratory insertion events of alkyne into Rh–C bond occur successively, both with complete regioselectivity. This method is particularly useful for synthesis of polyarenes with different substituents, which has not been reported with conventional protocol. A mechanism has been proposed to explain the observed data.

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1. Introduction

Great advancement has been made in transition metal catalyzed C–H bond activation and functionalization in the past 20 years [1–4]. The merits of direct C–H bond functionalization could reach its full extension only when site selective is achieved because there are almost always multiple C–H bonds in any organic substrate. The most common and successful strategy to address this selective challenge is using substrates containing coordinating ligands, namely directing groups [5,6]. By coordinate to transition metal, the directing group could deliver the catalytic center to a proximal C–H bond and therefore force the C–H bond-activating event to occur in a controlled manner. A plenty of directing groups have been devised for this purpose, and due to its vast structural diversity, the N-containing directing groups constitute the major and most important part. These N-containing directing groups span from various aromatic N-heterocycles, amines, amides, imides and imines to hydrazones, oximes, triazoles, and ureas, etc.[7–40].

Polycyclic aromatic compounds have been found increasing applications in functional materials in virtue of their excellent

electro- and photo-chemical properties [41–45], which very often could be modulated through the introduction of multiple substituents on the arene core [46–49]. Metal catalyzed coupling of arene with two fold internal alkynes provides an efficient arene homologation method for poly-substituted polycyclic aromatic compounds [50–61]. Direct site selective homologation of un-preactivated arenes, which involves double C–H activation is highly appreciated as this method can provide polycyclic aromatic compounds in both efficient and controlled manner from easily accessible un-functionalized arenes [62–65]. Here, we would like to report a urea group directed arene homologation catalyzed by Rh(III) complex employing either symmetric or unsymmetrical internal alkynes as coupling partners.

2. Experimental

2.1. General

^1H NMR and ^{13}C NMR spectra were recorded using Bruker AV-300/AV-400/AV-500 spectrometers. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator and/or by exposure to phosphomolybdic acid followed by brief heating with a heat gun. Liquid chromatography (flash chromatography) was performed on 60 Å (40–60 μm) mesh silica gel (SiO_2). All reactions were carried out under nitrogen or argon with anhydrous solvents in flame-dried

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glassware, unless otherwise noted. All reagents were commercially obtained and, where appropriate, purified prior to use.

2.2. General procedure for the homologation of aryl ureas

A mixture of the diphenylacetylene **2** (1.0 mmol, 2.5 eq.), **1** (0.4 mmol), [Cp*RhCl₂]₂ (6.2 mg, 0.01 mmol, 2.5 mol%), Cu(OAc)₂ (188 mg, 1 mmol, 2.5 eq.), and AgSbF₆ (28 mg, 0.08 mmol, 20.0 mmol %) were weighed into a Schlenk tube equipped with a stir bar. *t*-AmOH (2 mL) was added and the mixture was stirred at 120 °C for 24 h under N₂ atmosphere. The reaction mixture was extracted with DCM for three times, and the combined organic layers were then dried over anhydrous Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 3:1 then 2:1 to afford the desired product **3**.

Characterization and spectra for new compounds are compiled in Supporting information.

3. Results and discussion

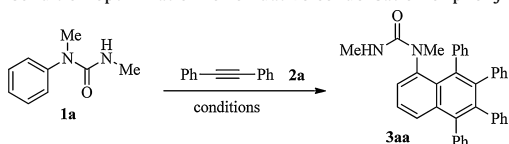
Our study commenced with urea **1a** and diphenyl acetylene **2a** (Table 1). Using an effective protocol disclosed by Fagnou team, several popular transition metal catalysts for oxidative C–H functionalization were explored. Pd(OAc)₂ and [RuCl₂(*p*-Cymene)]₂ failed to promote any reaction (entries 1–3). [Cp*RhCl₂]₂ activated by AgSbF₆ did catalyze the desired arene homologation reaction and *t*-AmOH is the solvent of choice for good yield (entries 4 and 5). It was also found that Cu(OAc)₂ was a necessary oxidant

and AgSbF₆ was a critical additive for this reaction to proceed smoothly (entries 5–7).

With the optimal conditions in hand, an array of urea substrates **1** were submitted to the reaction with diphenyl acetylene **2a** (Table 2). *Meta* substituted ureas, such as **1b** and **1c** were feasible substrates to give 5, 6, 7, 8-tetraphenyl naphthalene **3ba** and **3ca** in yields of more than 60% (entries 2–3). On the other hand, *ortho*- and *para*- substituents decreased the yield dramatically, as both tetraphenyl naphthalenes **3da** and **3ea** were obtained from **1d** to **1e** in less than 20% yields (entries 4–5). *N,N*-diphenyl urea **1f** condensed with diphenyl acetylene to give rise to **3fa** in 27% yield (entry 6). These outcomes may be the results of collective steric effects of both aryl substituents and bulky Cp* ligand on metal center, which will be discussed later on.

Further studies using unsymmetrical alkynes as the homologation partners highlight the virtue of this protocol (Table 3). Condensation of phenyl methyl acetylene **2b** with urea **1a**, **1b**, **1c** gave related 5,8-dimethyl-6,7-diphenyl naphthalenes **3ab**, **3bb**, **3cb** in 60–70% yields. The structure of **3ab** was established by extensive NMR experiments including, 2D ¹H–¹H Noesy experiments. The selectivity demonstrated by these reactions is amazing as only one single regioisomer is produced out of four possible isomers. Moreover, to our delight, *ortho* substituted phenyl urea **1e** achieved a much higher yield for 5,8-dimethyl-6,7-diphenyl naphthalene **3eb** (Table 3, entry 4, 63%) than the yield for 5,6,7,8-tetraphenyl naphthalene **3ea** (Table 2, entry 5, 18%). Methoxymethyl phenyl acetylene **2c** is also condensed with **1a** to give **3ac** in 51% yield with exclusive regioselectivity, while alkynes **2d** and **2e** are not feasible coupling partners for this reaction.

Table 1
Condition optimization for oxidative condensation of phenyl urea with alkyne.^a

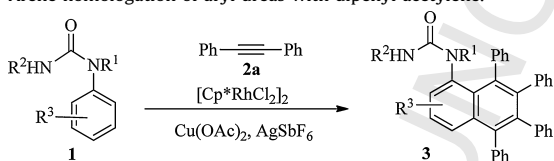


Entry	Catalyst	Oxidant	Additive	Solvent	Yield (%) ^b
1	Pd(OAc) ₂	Cu(OAc) ₂	–	<i>t</i> -AmOH	–
2	[RuCl ₂ (<i>p</i> -Cym)] ₂	Cu(OAc) ₂	–	<i>t</i> -AmOH	–
3	[RuCl ₂ (<i>p</i> -Cym)] ₂	Cu(OAc) ₂	–	DCE	–
4	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	AgSbF ₆	toluene	20
5	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	AgSbF ₆	<i>t</i> -AmOH	50
6	[Cp*RhCl ₂] ₂	Air	AgSbF ₆	<i>t</i> -AmOH	–
7	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	–	<i>t</i> -AmOH	complex

^a Reaction conditions: **1a** (0.4 mmol, 1.0 eq.), **2a** (1.0 mmol, 2.5 eq.), oxidant air or Cu(OAc)₂ (1 mmol, 2.5 eq.) and catalyst (0.01 mmol, 2.5 mol%) in *t*-AmOH (2.5 mL) was heated to 120 °C in a Schlenk tube for 24 h;

^b Isolated yield.

Table 2
Arene homologation of aryl ureas with diphenyl acetylene.^a



Entry	1	R ¹	R ²	R ³	Product	Yield (%) ^b
1	1a	Me	Me	H	3aa	50
2	1b	Me	Me	3-Me	3ba	61
3	1c	Me	Me	3-Cl	3ca	63
4	1d	Me	Me	4-Me	3da	17
5	1e	Me	Me	2-Cl	3ea	18
6	1f	Ph	Pr	H	3fa	27

^a Reaction conditions: **1** (0.4 mmol, 1.0 eq.), **2a** (1.0 mmol, 2.5 eq.), Cu(OAc)₂ (1 mmol, 2.5 eq.), AgSbF₆ (0.02 mmol, 5 mol%), and [Cp*RhCl₂]₂ (0.01 mmol, 2.5 mol%) in *t*-AmOH (2.5 mL) was heated to 120 °C in a Schlenk tube for 24 h under N₂;

^b Isolated yield.

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