



Divergent synthesis of flavones and aurones via base-controlled regioselective palladium catalyzed carbonylative cyclization

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ABSTRACT

A regioselective approach for construction of 5-membered and 6-membered flavonoid is established by Pd catalyzed carbonylative cyclization of 2-iodophenol with terminal alkynes using different amine bases under mild reaction condition. The catalytic experiments found that piperazine preferentially accelerate 6-endo cyclization, and triethylamine mediated Pd catalyzed 5-exo cyclization. Under optimized reaction condition, Pd catalyzed carbonylative protocol successfully applied for the diverse structures of 39 examples in good to excellent yield and regioselectivity.

1. Introduction

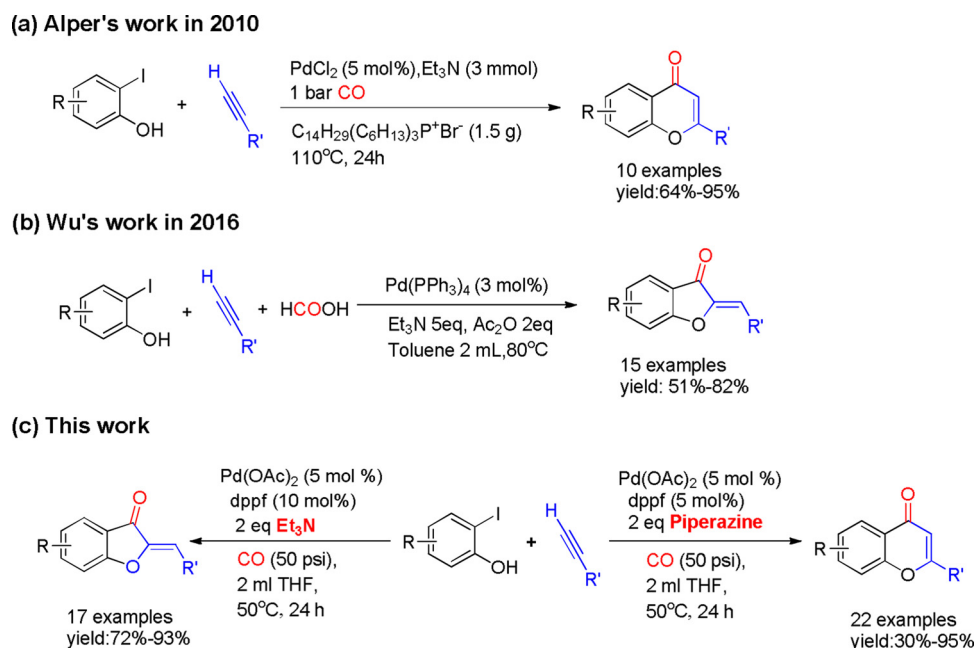
Flavones and aurones are two important branches of flavonoids since they exhibit a wide range of biological activities. Due to the anti-inflammatory [1], anti-cancer [2], antioxidant activities of flavonoids [3], and their pharmaceutical applications [4], many synthetic methods for those heterocyclic compounds were developed in recent years. For flavones, the synthetic methods are following as carbonylation of phenols and internal alkynes [5], base/acid mediated cyclization of *o*-hydroxyketone or 2'-hydroxychalcones [6], Lewis base catalyzed tandem acyl transfer-cyclization [7], cyclization of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones [8], carbonylative coupling of aryl bromides with 2-hydroxyacetophenones [9], annulation of salicylaldehydes with alkynes or benzaldehyde [10], and dehydrogenation/oxidative Boron-Heck coupling of chromanone with arylboronic acid pinacol esters [11]. For aurones, the methods are including the ring closure of *o*-hydroxyketone [12] and oxidation/cyclization of 2-(1-hydroxy-3-phenylprop-2-ynyl)-phenol [13]. These methods are good supplement to construct chromones' skeletons of flavones and aurones, but a straightforward synthetic procedure using simple substrates under mild reaction condition is still highly desirable [14].

Palladium catalyzed carbonylation reaction has drawn much interest for developing new cyclization reactions [15]. Chiusoli et al. [14m] firstly utilized Pd-catalyzed three component annulation of 2-halophenols, terminal alkynes and CO for the synthesis of aurones. Yang et al. [14i] designed the catalyst system of PdCl₂(Ph₃P)₂, thiourea

and dppp for the regioselective carbonylative annulation of iodophenol and acetylenes, which avoided the five-membered aurones formation. Capreeta et al. [14g] employed PA-Ph (1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane) as coligand for microwave-assisted Pd catalyzed one-pot Sonogashira-carbonylation-annulation. In the ionic liquids of phosphonium salt, Alper et al. [14f] established ligand-free palladium catalyzed carbonylative annulation reaction for selective synthesis of flavones. Li et al. [14e] demonstrated the potential of NHCs as highly efficient ligands by which Pd(II) benzimidazolin-2-ylidene were identified as efficient complexes for catalytic cyclo-carbonylation of *ortho*-functionalized aryl iodides. Wu et al. utilized Pd/C as heterogeneous catalyst for the cyclocarbonylation of 2-iodophenol with terminal acetylenes to synthesis of flavones in presence of CO (15 bar) [14a], while Pd(PPh₃)₄ catalyzed carbonylative synthesis of aurones were achieved by in situ CO generation from formic acid and Ac₂O [14b]. Pd catalyzed carbonylative annulation reactions showed interesting solvent effects on the regioselectivity. PdCl₂(PPh₃)₂ and benzimidazole-triazole catalyzed regioselective carbonylative annulation of 2-bromophenols and terminal alkynes afforded flavones and aurones in *i*-Pr₂NH and *n*-Pr₂NH, respectively [14d]. The solvent switchable regioselective carbonylative coupling reaction of 2-iodophenols and terminal alkynes using Pd(0)APTES@K10 (APTES = (3-aminopropyl)-triethoxysilane) afforded flavones and aurones in DME and DMF, respectively [14c]. These precedents clearly demonstrated that varying Pd catalyst system or solvents are able to control the outcome of Pd catalyzed cyclization. To develop simple but efficient Pd

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Scheme 1. Recent progress on Pd-catalyzed carbonylative cyclization for flavonoid synthesis.

Table 1
Piperazine accelerated Pd catalyzed three-component carbonylative cyclization^[a].

Entry	Pd/L	Solvent	Yield ^[b]	Selectivity(3:4)
1	Pd(OAc) ₂ /-	CH ₃ CN	41%	63:37
2	PdCl ₂ /-	CH ₃ CN	34%	59:41
3	Pd(OAc) ₂ /PPh ₃	CH ₃ CN	47%	82:18
4	Pd(OAc) ₂ /Xantphos	CH ₃ CN	72%	92:8
5	Pd(OAc) ₂ /dppf	CH ₃ CN	80%	94:6
6	Pd(OAc) ₂ /dppp	CH ₃ CN	69%	88:12
7	Pd(OAc) ₂ /dppb	CH ₃ CN	62%	85:15
8	Pd(OAc) ₂ /dppf	CH ₃ CH ₂ OH	44%	73:27
9	Pd(OAc) ₂ /dppf	DMF	66%	91:9
10	Pd(OAc) ₂ /dppf	DMSO	70%	90:10
11	Pd(OAc) ₂ /dppf	PhMe	60%	75:25
12	Pd(OAc) ₂ /dppf	dioxane	80%	94:6
13	Pd(OAc) ₂ /dppf	THF	86%	> 99:1

[a] Reaction conditions: 2-iodophenols (0.5 mmol), alkyne reagent (0.6 mmol), Pd source (5 mol%), ligand (10 mol%), piperazine (2.0 eq) and solvent (2 mL) was stirred at 50 °C for 24 h. [b] The yield and selectivity was determined by ¹H NMR.

catalyzed protocols continue to be of great interest for selective preparation these chromones (Scheme 1). In addition, to reduce CO pressure and reaction temperature, and avoiding large excess of strong bases are still challenge to establish safe and mild Pd catalyzed carbonylative annulation methodology. With this goal and our recent progress on Pd catalyzed carbonylative C-C coupling reactions [16], herein we wish to report an efficient Pd catalyzed divergent synthesis of flavones and aurones by tuning bases under mild reaction condition. By using piperazine and triethylamine as base, respectively, Pd(OAc)₂-dppf catalyzed carbonylative annulation of functionalized 2-iodophenols and terminal alkynes afforded 5-membered aurones and 6-membered flavones with satisfactory yield and selectivity. The control experiments unveiled that piperazine accelerated 6-endo cyclization of the intermediate of alkynyl ketone whilst triethylamine mediated Pd catalyzed 5-exo cyclization.

2. Experimental

2.1. General materials and methods

All manipulations were performed in the autoclave under CO atmosphere. Commercially available reagents were used without further purification. NMR spectroscopic data were recorded in CDCl₃ or [d₆] DMSO with a 400 or 600 MHz instrument, and TMS was used as the internal standard; data are reported as chemical shift (ppm), multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)], coupling constants in Hz, and integration. HRMS data were recorded in the ESI mode with a TOF mass analyzer. Flash column chromatography was performed on silica gel (200–300 mesh).

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