Dr. A Chandrasekhar Reddy
Department of Chemistry
IIT Madras, INDI

HR Manager
Intonation Research Laboratories Pvt Ltd
INDIA

Objective: Application for a Challenging Position.

Dear Madam/Sir,

My name is A Chandrasekhar, and I graduated from **Indian Institute of Technology Madras (IIT Madras)** Chennai, India with a Ph.D. degree in organic chemistry under the supervision of **Prof. S. Sankararaman**. My thesis entitled "**Pd-Catalyzed *C*−*X* and *C*−*H* Carbonylative Annulation Strategy in Heterocycle Synthesis**". I have worked as a post-doctoral scientist at **Hong Kong Baptist University** (HKBU) under the guidance of **Prof. Dik-Lung Ma.** I would very much like to work in a challenging position at your reputed industry to upgrade my skills, knowledge and expertise as a chemist wherein my educational background along with my synthetic, analytical and experimental skills will add value to the team and the organization. My Ph.D. work involves Pd-catalyzed carbonylative annulations for the synthesis of various biologically active heterocyclic compounds. I would be extremely glad if you would consider my application for a challenging position. I would be happy to answer any questions if you have.

In my Ph. D. work, The carbonylative Sonogashira coupling followed by intramolecular aldol reaction was introduced for the synthesis of 3-aryl-4-(arylethynyl)-2*H*-chromen-2-ones in the presence of Pd(0) as the catalyst. Pd(0)-catalyzed carbonylative annulation reaction of 1-(2-iodoaryl)-3-aryltriaz-1-enes resulted in the formation of 3-arylbenzo-1,2,3-triazin-4(3*H*)-ones with high selectivity and in excellent yields. Pd(II)-catalyzed oxidative *C*−*H* carbonylative annulation of *N*,1-diaryl-1*H*-tetrazol-5-amines and *N*,4-diaryl-4*H*-1,2,4-triazol-3-amines gave the corresponding triazole and tetrazole fused quinazolinones. The catalytically active *C*−*H* activated intermediate dimeric Pd complex was isolated and characterized. Based on the isolation of the intermediate and observed kinetic isotope effects, a mechanism has been proposed for this *C*−*H* activated direct carbonylative annulation reaction. A methodology involving Pd catalyzed direct $C(sp^2)-H$ bond carbonylation of indoles at C2 position is introduced for the first time, for the synthesis of indolo[1,2,-a]quinoxlin-6(5*H*)-ones. In my Post-Doc work, Ir complex based inhibitors were synthesized.

I conclude with the hope that I have been able to convey myself appropriately. The summary of my research work is given in the last part of my curriculum vitae (C.V.) for your kind perusal. If I find myself fortunate in this communication, I will be eager to join in the position at the earliest possible session at your end. In anticipation of your consideration, I look forward to joining your company for a fruitful and exciting career life.

Sincerely,

A Chandrasekhar Reddy

Curriculum Vitae

Personal Details

Name	Dr. A Chandrasekhar Reddy
Address	Lab No. 154, Department of Chemistry Indian Institute of Technology Madras, Chennai, INDIA
Date of Birth	20.05.1988
Nationality	Indian
Email	acr.chem@gmail.com
Contact No	+91 9176476594
Marital Status	Single
ORCID iD	0000-0001-8864-772X

Education

2019-2020	Hong Kong Baptist University (HKBU), Hong Kong **Postdoctoral Studies,** adviser: Prof. Dik-Lung Ma
2013-2018	Indian Institute of Technology Madras (IIT Madras) (The Topmost Institute in India, Rank 1 by NIRF, MHRD Govt. of India) Chennai, India **Ph.D.** in Organic Chemistry, adviser: Prof. S. Sankararaman (**Thesis title**: *Pd Catalyzed C−X and C−H Carbonylative Annulation Strategy in Heterocycle Synthesis*)
2008-2010	S. V. University, Tirupathi, Andhra Pradesh, India **Master of Science (M.Sc.)** in Organic Chemistry, First Division
2005-2008	S. V. University, Tirupathi Andhra Pradesh, India **Bachelor of Science (B.Sc.), (C.P.Z),** First Division

2003-2005	Sri Srinivasa Junior College, Renigunta (Board of Intermediate Education) Andhra Pradesh, India **Intermediate (10+2) (Bi.P.C),** First Division
2003	Z. P. High School (Boys), Renigunta (Board of Secondary Education) Andhra Pradesh, India). **SSC (X^{th} Class),** First Division

Research Experience

2013-2018 ***PhD Studies with Prof. S. Sankararaman***

C−X carbonylation: Carbonylative Sonogashira coupling followed by intramolecular aldol reaction for the synthesis of 3-aryl-4-(arylethynyl)-2*H*-chromen-2-ones. Carbonylative annulation of 1-(2-haloaryl)-3-aryltriaz-1-enes for the formation of 3-arylbenzo-1,2,3-triazin-4(3*H*)-ones.

C−H carbonylation: Oxidative *C−H* carbonylative annulation of *N*,1-diaryl-1*H*-tetrazol-5-amines and *N*,4-diaryl-4*H*-1,2,4-triazol-3-amines for synthesis quinazolinones. Direct C(sp^2)−H bond carbonylation of unprotected 2-(1*H*-indol-1-yl)anilines for the synthesis of indolo[1,2,-a]quinoxlin-6(5*H*)-ones.

2018-2019 ***Research Associate with Prof. S. Sankararaman***

Direct C(sp^2)−H bond carbonylation of protected 2-(1*H*-indol-yl)anilines at C_2 position for the synthesis of indolo[1,2,-a]quinoxlin-6(5*H*)-ones and the isolation and characterization of catalytically active *C–H* activated intermediate of 2-(5-methoxy 1H-indol-1-yl)-N,4-dimethylaniline

2019-2020 ***Postdoctoral Studies with Prof. Dik-Lung Ma***

Synthesis and characterization of peptide and macro organic ligand conjugated iridium(III) complexes and as an inhibitors.

Supervision, Tutor and Teaching Experience

Supervision of Junior Researchers

At HKBU, Hong Kong

05-11/2019 Chun Wu (Ph.D. Scholar)

09/2019-01/2020 Guodong Li (Research Assistant)

At IIT Madras, India

07/2014-04/2015 Poonam Debnath (Master Thesis)

07/2015-04/2016 Anurag Singh (Master Thesis)

06-08/2016 Subba Reddy (Master internship)

06-08/2017 E. Sharmila (Master internship)

0-04/2019 Priya. V (Ph.D. Scholar)

Tutor & Teaching Experience

2014-2017 Teaching assistantship at Indian institute of technology Madras, tutor for undergraduate courses and organic lab.

2017 Teaching assistantship in national programme on technology enhanced learning (NPTEL) funded by the ministry of HRD, Govt. of India at Indian institute of technology Madras.

2010-2012 Faculty at Sri Chaitanya Bharathi Jr college Tirupati

Skills

- Design and complete a project independently or as a team. Analysis and accurate interpretation of spectral data.
- Acquired skills in carrying out multistep reaction sequence. Expertise in isolation of pure compounds through gravity column chromatography or by other purification techniques and performing reactions in both small and large scale.
- Well experienced in handling carbon monoxide (CO gas), hydrogen gas, dry reactions and various sensitive reagents.
- Well experienced in the synthesis of organic ligand conjugated Ir(III) complex based inhibitors in pure form.
- Diligent in conducting organic lab experiments and recording experimental details.

- Actively involved in group discussion and presentations pertaining to the project and used every opportunity to educate myself and group members by sharing information.
- Lab tutor, teaching and supervision experience, and good communication skills.
- Good knowledge of Microsoft Office (Word, Excel, PowerPoint), Chem Draw and other advanced digital tools.

Instruments Handled

- FT NMR spectrometer (Bruker AV- 400 MHz & 500 MHz).
- FT-Infra-Red spectrophotometer (JASCO FT/IR-4100).
- GC/MS, HPLC Chromatography.

Awards Received

- Awarded **"Postdoctoral Fellowship"** (April 2019– April 2020) sponsored by Hong Kong Baptist University, Govt. of Hong Kong.
- Awarded **"Institute Research Associate Fellowship"** (Oct 2018 – April 2019) sponsored by IIT Madras, Govt. of India.
- Awarded "**CSIR-UGC Senior Research Fellowship**" (CSIR-UGC SRF), IIT Madras (July 2015 – July 2018) sponsored by UGC, New Delhi, Govt. of India.
- Awarded "**CSIR- UGC Junior Research Fellowship**" (CSIR- UGC JRF), IIT Madras (July 2013 – July 2015) sponsored by UGC, New Delhi, Govt. of India.
- Awarded "**Junior Research Fellow**" in the national level exam conducted by CSIR-UGC-NET, India with all India rank 91 in June 2012.
- Awarded "**Lectureship (NET)**" in the national level exam conducted by CSIR-UGC-NET, India with all India rank 33 in Dec 2011, 91 in June 2012, 45 in Dec 2012.

Publications

1. **Chandrasekhar, A**.; Ramkumar, V.; Sankararaman, S. *Eur. J. Org. Chem.* **2016**, 2016, 4041; "Highly Selective and Modular Synthesis of 3-Aryl-4-(arylethynyl)-2*H*-chromen-2-ones from 2-Iodoaryl 2-Arylacetates through a Carbonylative Sonogashira Coupling intramolecular Aldol Cascade Reaction." DOI: 10.1002/ejoc.201600569.

   (Ramkumar, V (Technician) Contribution: XRD data).

2. **Chandrasekhar, A**.; Sankararaman, S. *J. Org. Chem*. **2017**, *82*, 11487. "Selective Synthesis of 3-Arylbenzo-1,2,3-triazin-4(3*H*)-ones and 1-Aryl-(1*H*)-benzo-1,2,3-triazoles from 1,3 Diaryltriazenes Through Pd(0) Catalyzed Annulation Reactions." DOI: 10.1021/acs.joc.7b02023.

3. **Chandrasekhar, A**.; Ramkumar, V.; Sankararaman, S. *Org. Biomol. Chem*. **2018**, *16*, 8629; "Palladium Catalyzed Carbonylative Annulation of the C(sp^2)-H bond of *N*,1-Diaryl-1*H*-tetrazol-5-amines and*N*,4-Diaryl-4*H*-triazol-3-amines to Quinazolinones." DOI: 10.1039/c8ob02516a.

   (Ramkumar, V (Technician) Contribution: XRD data).

4. **Chandrasekhar, A**.; Sankararaman, S. *Org. Biomol. Chem*. **2020**, *18*, 1612; "Synthesis of Indolo- and Pyrrolo[1,2-a]quinoxalinones through Palladium-Catalyzed Oxidative Carbonylation of C_2 Position of Indole." DOI: 10.1039/c9ob02703c.

5. **Chandrasekhar, A;** Ma, D. −L.; et all. *To be Communicated*, **2020**; Synthesis and characterization of peptide and other organic ligand conjugated Ir(III) complexes and as inhibitors.

Conferences

- National Organic Symposium Trust (**XII J-NOST-2016**), 24th- 27th Nov 2016; CSIR-Central Drug Research Institute, Lucknow, **India**.

  (Title: Highly Selective and Modular Synthesis of 3-Aryl-4-(arylethynyl)-2*H*-chromen-2-ones through a Carbonylative Sonogashira Coupling intramolecular Aldol Cascade Reaction.)

- International Society of Heterocyclic Chemistry (**26th ISHC Congress**), 03rd - 08th Sep 2017; University of Regensburg, Regensburg**, Germany**.

  (Title: Selective Synthesis of 3-Arylbenzo-1,2,3-triazin-4(3*H*)-ones and 1-Aryl-(1*H*)-benzo-1,2,3-triazoles from 1,3 Diaryltriazenes through Pd(0) Catalyzed Annulation Reactions.)

- National Organic Symposium Trust (**XIII J-NOST-2017**), 09th- 12th Nov 2017; CSIR-Central Banaras Hindu University, Varanasi, **India**.

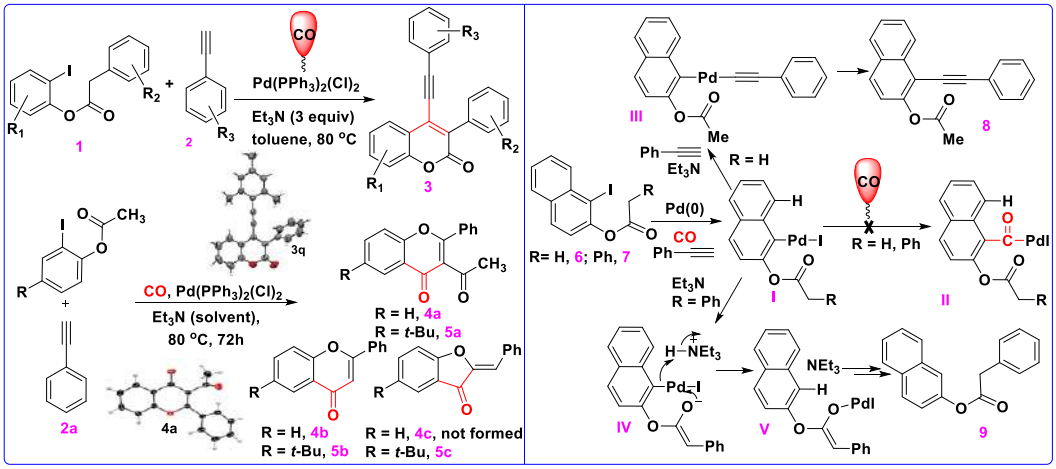
  (Title: Pd-Catalyzed Carbonylative Annulation of C(sp^2)-H bond of diaryl amino triazole & tetrazole)

Summary of Ph.D. Research Work

CHAPTER-I

Synthesis of 3-Aryl-4-(arylethynyl)-2*H*-chromen-2-ones from 2-Iodoaryl 2-Arylacetates through a Carbonylative Sonogashira Coupling-Intramolecular Aldol Cascade Reaction.

2*H*-Chromen-2-one (coumarin) and its derivatives are found in nature, especially in the plant kingdom. They are an important class of compounds as they display a wide range of biological activities. Herein, 3-Aryl-4-(arylethynyl)-2*H*-chromen-2-ones(coumarins) are synthesized from corresponding iodoarylarylacetates and arylacetylenes in presence of catalytic amount of $Pd(PPh_3)_2Cl_2$ under basic conditions in toluene under balloon pressure of CO at 80 ^oC. Coumarin, which contains a terminal acetylene group was also synthesized and it could serve as a starting material in synthesis designed for further structural diversity. The feasibility of a one pot synthesis of **3** was then investigated by sequentially adding the reagents of the two steps. When 2-iodoaryl acetates were treated separately with phenylacetylene in Et_3N as the solvent, a mixture of products were formed(Scheme**1.1**).



Scheme 1.1 Synthesis of 3-Aryl-4-(arylethynyl)-2*H*-chromen-2-ones.

The attempted synthesis of naphthalene substituted coumarin from corresponding iodo starting material under the standard reaction conditions failed to furnish the expected naphthyl fused 2*H*-chromen-2-one derivative. Instead, the reaction yielded the product of deiodination. Based on control experiments a possible mechanism for the formation of deiodinated product is proposed.

We have developed a modular carbonylative annulation method for the synthesis of 3-aryl-4-(arylethynyl)-2*H*-chromen-2-ones from 2-iodoaryl 2-arylacetates and arylacetylenes.

References:

1. Chandrasekhar, A.; Ramkumar, V.; Sankararaman, S. *Eur. J. Org. Chem*. **2016**, 2016, 4041.

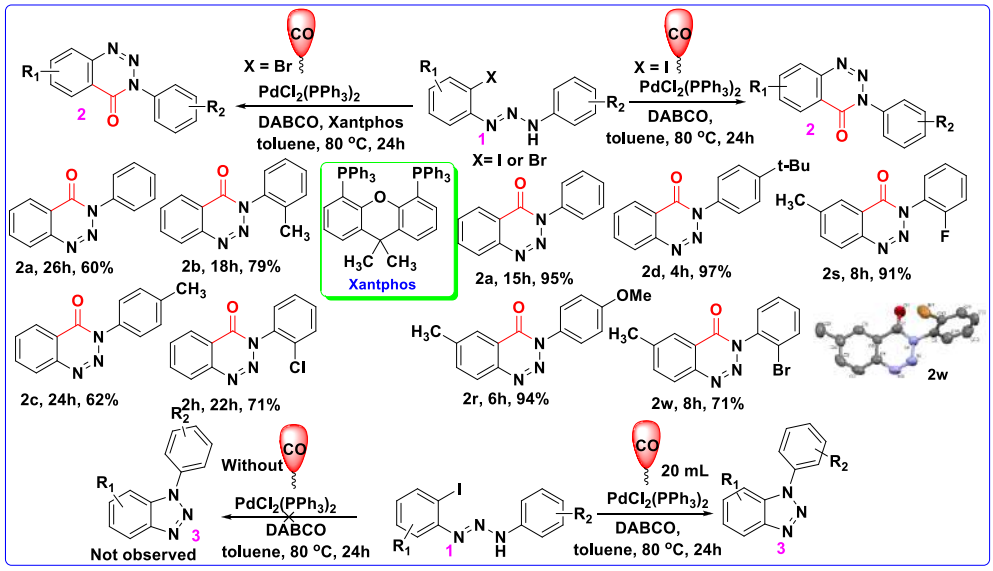
2. D. V. Kadnikov, R. C. Larock, *Org. Lett.* **2000**, *2*, 3643.

3. M. Yoshida, K. Saito, Y. Fujino, T. Doi, *Chem. Commun.* **2012**, *48*, 11796.

CHAPTER- II

Pd(0) Catalyzed Carbonylative Annulation of 1,3-Diaryltriazene Derivatives for Facile and Highly Selective Synthesis of 3-Arylbenzo[1,2,3]triazin-4(3*H*)-ones.

Benzo[1,2,3]triazin-4-one is an important heterocyclic scaffold in medicinal chemistry. Derivatives of benzo[1,2,3]triazin-4-ones exhibit a wide variety of biological activities. 3-Arylbenzo[1,2,3]triazin-4(3*H*)-ones(**2**) were synthesized from 1-(2-haloaryl)-3-arylltriaz-1-enes in presence of $Pd(PPh_3)_2Cl_2$ and DABCO as base under balloon pressure of CO in toluene at 80 °C. Using optimized reaction conditions a variety of 3-arylbenzo[1,2,3]triazin-4(3*H*)-ones were synthesized from corresponding halo compounds in good to excellent yields (Scheme **2.1).**



Scheme 2.1 Pd Catalyzed annulation of 1-(2-haloaryl)-3-arylltriaz-1-ene under CO gas

In order to make the methodology more versatile, carbonylative annulation of 1-(2-bromophenyl)-3-arylltriaz-1-enes to the corresponding 3-arylbenzo[1,2,3]triazin-4(3*H*)-ones was investigated in presence of xantphos as a ligand. To examine the efficiency of the carbonylation reaction in gram scale, the reaction was carried out with 1.1 g (3.4 mmol) of 1-(2-iodophenyl)-3-phenyltriaz-1-ene and desired product was obtained in 92% yield. A variety of 1-aryl-1*H*-benzo[d][1,2,3] triazoles were synthesized from 1-(2-iodoaryl)-3-arylltriaz-1-enes in the presence of PPh_3or catalytic amount of CO but otherwise under identical conditions. Based on some control experiments and observations a plausible mechanism for the formation of benzo[1,2,3]triazin-4(3*H*)-ones (**2**) in the presence of CO and 1,2,3-benzotriazoles (**3**) in catalytic amount of CO is proposed.

In this chapter a new methodology for the synthesis of 3-arylbenzo[1,2,3]triazin-4(3*H*)-ones from corresponding iodo and bromotriazenes has been developed.

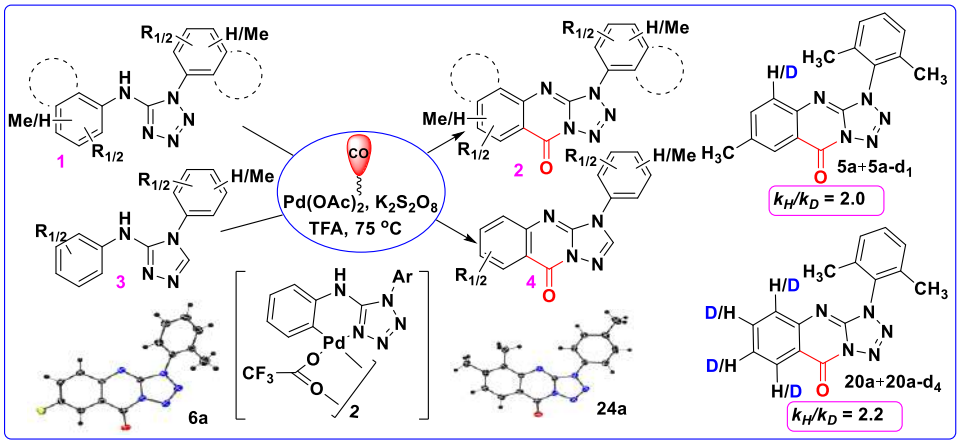
References:

1. Chandrasekhar, A.; Sankararaman, S. *J. Org. Chem.* **2017**, *82*, 11487.
2. Cho, C. S.; Lee, J. W.; Lee, D. Y.; Shim, S. C.; Kim, T. J. *Chem. Commun*. **1996**, 2115.
3. Yin, J.; Buchwald, S. L. *J. Am. Chem.* Soc. **2002**, *124*, 6043.

CHAPTER- III

Pd(II) Catalyzed Direct Carbonylative Annulation of C(sp^2)-H bond of *N*,1-Diaryl-1*H*-tetrazol-5 amines and *N*,4-Diaryl-4*H*-triazol-3-amines.

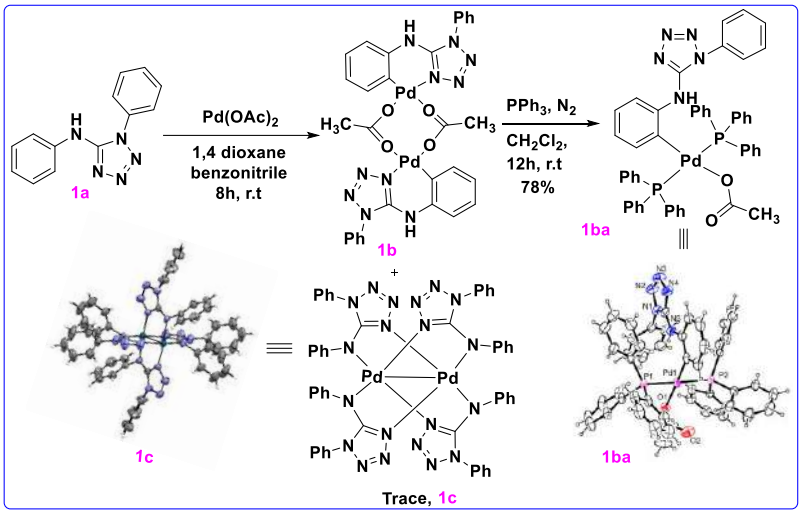
Quinazolinone is an important scaffold found in nature and exhibits wide range of biological activities including antibacterial, anti- fungal and anti-cancer activities. The Pd catalyzed direct carbonylation of C(sp^2)-H bond of *N*,1-diaryl-1*H*-tetrazol-5-amines was carried out in presence of $Pd(OAc)_2$ and $K_2S_2O_8$ as an oxidant in trifluroacetic acid (TFA) at 75 °C under CO balloon to give the corresponding carbonylative annulated 3-aryltetrazolo[5,1-*b*]quinazolin-9(3*H*)ones in good yields (Scheme **3.1**).



Scheme 3.1 Pd Catalyzed *ortho* C-H carbonylation of diarylaminotetrazoles and triazoles

The methodology developed was applied to the carbonylative annulation of *N*,4-diaryl-4*H*-1,2,4-triazol-3-amines. The triazole derivatives were found to be more reactive than the tetrazole derivatives and the corresponding 3-aryl-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-ones were obtained in high yields. To gain insight into the mechanism of the reaction, reaction intermediate that C−H activated cyclopalladated complex **1b** was isolated (Scheme **3.2**). In order to establish the involvement of **1b** in carbonylative annulation reaction, it was treated with carbon monoxide in TFA. The reaction of **1b** with CO proceeded smoothly to yield **2**. To understand the nature of C−H bond activation in carbonylation, intra and intermolecular kinetic isotope effect (KIE) were investigated. Based on these mechanistic studies, we

propose a plausible mechanism for the carbonylative annulation of *N*,1-diaryl-1*H*-tetrazol-5-amines. The heterocyclic moiety plays a dual role as directing group as well as internal nucleophile resulting in the annulation reaction.



Scheme 3.2 Formation and characterization of intermediate palladium complexes

A direct C-H activated carbonylative annulations of diarylaminotriazole and tetrazoles to the corresponding 3-aryltetrazolo[5,1-*b*]quinazolin-9(3*H*)ones and 3-aryl-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-ones has been investigated.

References:

1. Chandrasekhar, A.; Ramkumar, V.; Sankararaman, S. *Org. Biomol. Chem*. 2018, *16*, 8629.

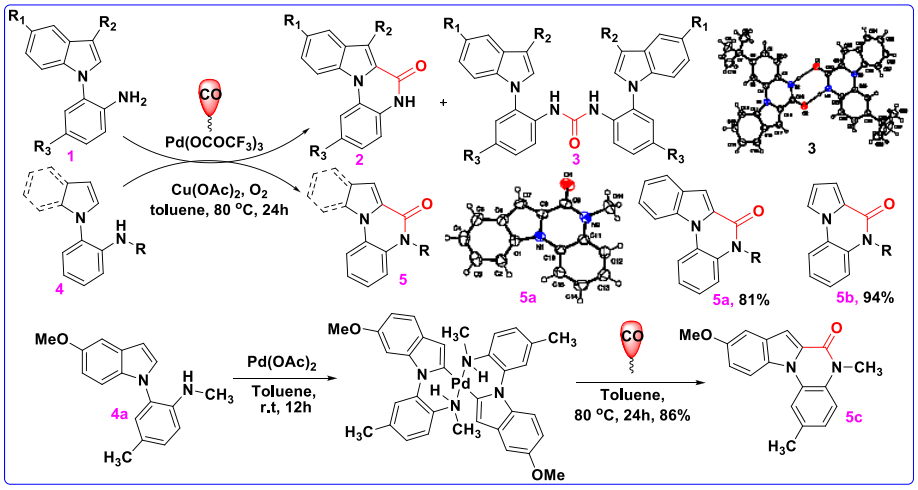
2. Giri, R.; Lam, J. K.; Yu, J. –Q. *J. Am. Chem. Soc*., **2010**, *132*, 686.

3. Luo, S.; Luo, F. -X.; Zhang, S.; Shi, Z. –J. *Angew. Chem., Int. Ed.*, **2013**, *52*, 10598.

CHAPTER- IV

Synthesis of Indolo[1,2-a]quinoxalinones and Pyrrolo[1,2-a]quinoxalinones through Palladium Catalyzed Oxidative Carbonylative Annulations of C_2 Position of Indole.

Compounds with indole fused quinoxalinone moiety as core structure are important due to their wide range of pharmacological properties. The investigation of CO insertion of 2-(1*H*-indol-1-yl)anilines(**1**) was started with the reaction of 2-(1*H*-indol-1-yl)aniline (**1a**) with carbon monoxide in presence of stoichiometric amount of $Pd(OAc)_2$ at 80 ^oC in toluene (Scheme **4.1**). It proceeded 100% conversion within 3h. The anticipated C_2 C−H carbonylative annulated product (**2a**) was obtained along with another possible product namely 1,3(2-(1*H*-indol-1-yl)phenyl urea (**3b**). With the optimal reaction conditions, scope of the formation of annulated product was investigated with various 2-(1*H*-indol-1-yl)anilines. Mechanism which involve for the formation of mixture of compounds was proposed.



Scheme 4.1 Carbonylation of 2-(1*H*-indol-1-yl)aniline.

The formation of urea was controlled by protecting the free amine group (Scheme **4.1**). However, *N*-acetyl or *N*-tosyl protected substrates did not react with carbon monoxide under standard reaction conditions as well as stoichiometric conditions. A variety of indolo[1,2-a]quinoxalinones and pyrrolo[1,2-a]quinoxalinones were synthesized from 2-(1*H*-indol-1-yl)-*N*-methylaniline and *N*-methyl-2-(1*H*-pyrrol-1-yl)anilines in the presents of $Pd(OCOCF_3)_2$ in toluene at 80°C. The intermediate which involves in this transformation was isolated and a possible reaction mechanism for the formation of compound **5c** was proposed.

In this chapter, a methodology involving Pd catalyzed direct C(sp^2)-H bond carbonylation of indoles at C_2 position introduced for the first time, for the synthesis of indolo[1,2,-a]quinoxalin-6(5*H*)-ones.

References:

1. Chandrasekhar, A.; Sankararaman, S. *Org. Biomol. Chem*. **2020,** *18*, 1612; DOI: 10.1039/c9ob02703c.

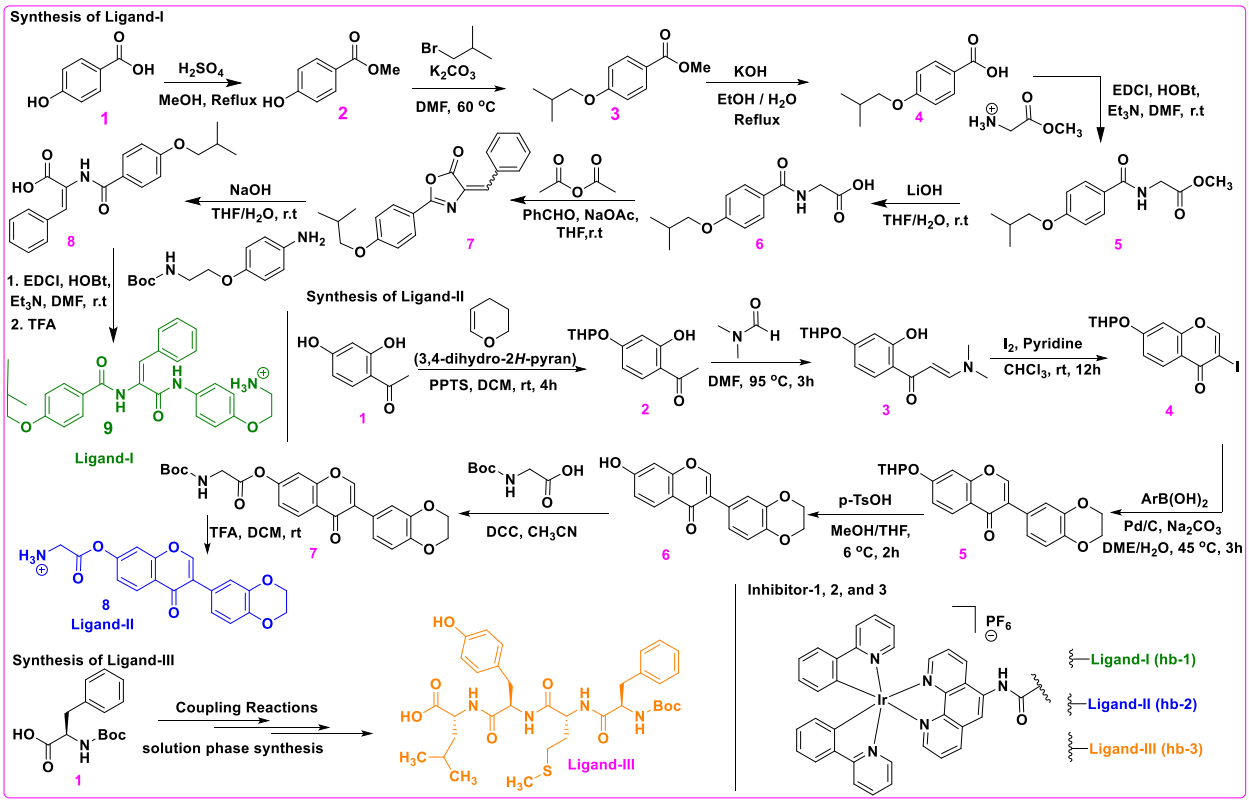
2. Mu, Q.-C.; Nie, Y. –X.; Bai, X. –F.; Chen, J.; Yang, L.; Xu, -Z.; Li, L.; Xia, C. –G.; Yu, L. –W. *Chem. Sci*., **2019**, *10*, 9292.

3. Tjutrins, J.; Arndtsen, B. *J. Am. Chem. Soc.* **2015**, *137*, 12050.

Summary of Post-Doc Research Work

Synthesis and characterization of peptide and macro organic ligand conjugated iridium(III) complexes and as an inhibitors.

Transition metal complexes are emerging as a promising class of luminophores for studying biological processes in living cells due to their long emission lifetime, large stokes shift and high photostability. In recent years, considerable effort has been made to develop transition metal complex–peptide conjugates as imaging probes such as cobaltocenium–peptide conjugates for studying cellular uptake, ruthenium short peptide conjugates for nuclear staining, and ruthenium-cyclic RGD peptide conjugates for targeting integrin receptors.



Scheme 5.1 Synthesis of Inhibitor-1, 2, and 3

Considering the additional favorable characteristics possessed by iridium(III) complexes including high quantum yields and tunable luminescence, the combination of an iridium(III) complex and a peptide or bio-active organic ligand may provide additional synergism for bioimaging applications. However, peptide functionalized iridium(III) complexes as bioimaging probes have not been widely explored. We are interested to study the peptide (Phe-Met-Tyr-Leu) and other macro organic ligand conjugated Ir(III) complexes. Inhibitor-1, 2, and 3 were synthesized and characterized by spectroscopic data.

References:

1. Ma, D. -L.; et all. *To be Communicated*, **2020.**
2. Wu, C.; Wu, K. -J.; Liu, J. -B.; Zhou, X. -M.; Leung, C. -H.; Ma, D. -L. *Chem. Commun*. **2019**, *55*, 6353.
3. Vellaisamy, K.; Li, G.; Wang, W.; Leung, C. -H.; Ma, D. -L. *Chem. Sci*., **2018**, *9*, 8171.

Declarations

I, hereby declare that all the information given above is true and correct to best of my knowledge and belief.

Dr. A Chandrasekhar Reddy

JOC The Journal of Organic Chemistry

Article

Cite This: J. Org. Chem. 2017, 82, 11487-11493

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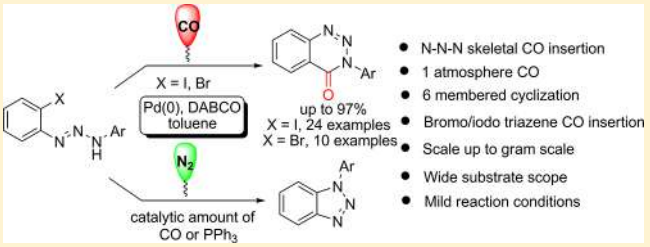
Selective Synthesis of 3-Arylbenzo-1,2,3-triazin-4(3*H*)-ones and 1-Aryl-(1*H*)-benzo-1,2,3-triazoles from 1,3-Diaryltriazenes through Pd(0) Catalyzed Annulation Reactions

Attoor Chandrasekhar and Sethuraman Sankararaman*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India

Supporting Information

ABSTRACT: Pd(0) catalyzed carbonylative annulation reaction of 1-(2-iodophenyl)-3-aryltriaz-1-enes in the presence of DABCO and 1 atm of carbon monoxide in toluene at 80 °C gave the corresponding 3-arylbenzo-1,2,3-triazin-4(3*H*)-ones with high selectivity and in excellent yields. Substrate scope of this reaction is demonstrated with 24 examples with various halo, alkyl, and alkoxy substituents on either of the aromatic rings. Bromo substituted triazenes were less reactive as starting materials toward the carbonylative annulation reaction and yielded 3-arylbenzo-1,2,3-triazin-4(3*H*)-ones in good to moderate yields in the presence of only xantphos as an additive. In the absence of CO (under N_2 atmosphere), the reaction did not proceed, and only starting material was recovered. However, in the presence of catalytic amount of CO or in the presence of Ph_3P in catalytic amounts as additives, the reactions proceeded to yield the corresponding 1-aryl-(1*H*)-benzo-1,2,3-triazoles selectively in good yields. On the basis of control experiments, a plausible reaction mechanism for the selective formation of 3-arylbenzo-1,2,3-triazin-4(3*H*)-ones in the presence of CO and1-aryl-(1*H*)-benzo-1,2,3-triazoles in the absence of CO through a common intermediate was proposed.



INTRODUCTION

Benzo-1,2,3-triazin-4(3*H*)-one is an important heterocyclic scaffold in medicinal chemistry. Derivatives of benzo-1,2,3-triazin-4(3*H*)-one exhibit a wide variety of biological activities such as sedative,[1] diuretic,[2] anesthetic,[3] antiarthritic,[4] antitubercular,[5] and antitumor activities.[6] The structures of a few representative examples of biologically active benzo-1,2,3-triazin-4(3*H*)-ones are shown in Figure 1.

Benzo-1,2,3-triazin-4(3*H*)-ones are also useful starting materials in organic synthesis for the synthesis of isoquinolones by metal catalyzed denitrogenative transannulation reactions with allenes and alkynes.[7] Conventionally, benzo-1,2,3-triazin-4(3*H*)-ones were synthesized through a multistep route from methyl anthranilates and anthranilamides using diazotization of the amino functional group (Scheme 1).[8] Recently, an oxidative annulation of 2-aminobenzamides with nitromethane using *tert*-butyl hydroperoxide and KI as oxidant[9] was reported. Copper catalyzed Ullmann type coupling of benzo-1,2,3-triazin-4(3*H*)-ones with aryl iodides and aryl boronic acids was reported for the synthesis of 3-arylbenzo-1,2,3-triazin-4(3*H*)-ones.[10] Pd

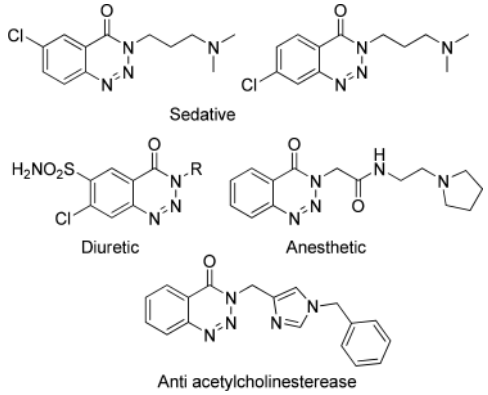
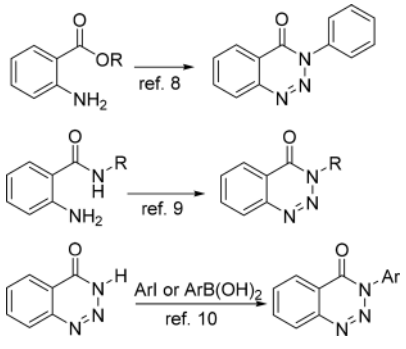


Figure 1. Representative examples of biologically active benzo-1,2,3-triazin-4(3*H*)-ones.

Scheme 1. Literature Methods for the Synthesis of Benzo-1,2,3-triazin-4(3*H*)-ones



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Synthesis of indolo- and pyrrolo[1,2-*a*]quinoxalinones through a palladium-catalyzed oxidative carbonylation of the C_2 position of indole†

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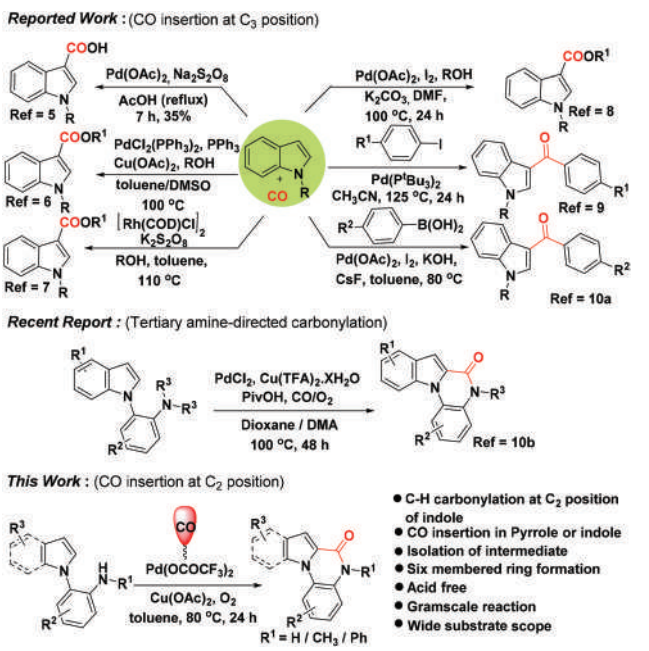
A methodology that involves the Pd-catalyzed direct C(sp2)–H bond carbonylation of the C_2 position of indole has been introduced for the synthesis of indolo[1,2-*a*]quinoxalin-6(5*H*)-ones. The methodology developed herein was used for the synthesis of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones. The reaction of *N*-substituted 2-(1*H*-indol-1-yl)anilines or 2-(1*H*-pyrrol-1-yl)anilines and carbon monoxide in the presence of $Pd(OCOCF_3)_2$ as a catalyst and $Cu(OAc)_2$ as an oxidant in toluene at 80 °C forms the corresponding quinoxalinones as exclusive products in good yields. The catalytically active C–H activated intermediate Pd complex was isolated and characterized for the first time which on exposure to CO gas in toluene at 80 °C gave the corresponding quinoxalinone derivative. On the basis of isolation of the intermediate, a possible mechanism has been proposed for the C–H activated direct carbonylative annulation of 2-(5-methoxy-1*H*-indol-1-yl)-*N*,4-dimethylaniline.

Introduction

Transition metal catalyzed CO insertion in organic halides or pseudo halides has become a powerful method for the synthesis of carbonyl compounds. A variety of carbonylated heterocyclic compounds were synthesized using a methodology that involves Pd-catalyzed carbonylative annulations[1] and they have received considerable attention since the seminal work of Heck.[2] More recently, transition metal catalyzed oxidative carbonylation of a C(sp2)–H bond has become the most atom economic and efficient way to incorporate carbon monoxide into hydrocarbons. The first direct oxidative carbonylation of arenes was introduced by Fujiwara in 1980 which involved electrophilic attack on an arene by palladium (II).[3] The concept of Pd-catalyzed carbonylation of the C(sp2)–H bond was used to synthesize various heterocyclic and acyclic compounds,[4] but it is limited to the carbonylation of the C(sp2)–H bond of indole derivatives. There are very few reports available on the oxidative carbonylation of the C_2 position of indoles (Scheme 1).

The first direct carbonylation of indoles was reported by Itahara in 1982.[5] 1-Acetylindole was treated with carbon monoxide in the presence of $Pd(OAc)_2$ and $Na_2S_2O_8$ as an oxidant



Scheme 1 Oxidative carbonylation of indole derivatives.

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Palladium catalyzed carbonylative annulation of the C(sp^2)–H bond of *N*,1-diaryl-1*H*-tetrazol-5-amines and *N*,4-diaryl-4*H*-triazol-3-amines to quinazolinones†

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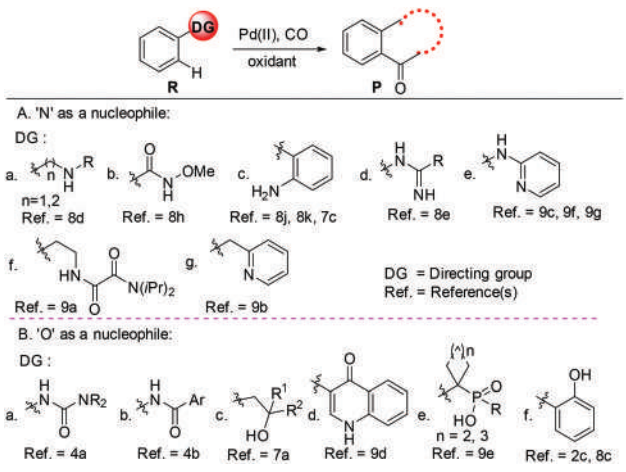
Pd(II) catalyzed direct C–H carbonylative annulation of *N*,1-diaryl-1*H*-tetrazol-5-amines and *N*,4-diaryl-4*H*-1,2,4-triazol-3-amines gave the corresponding triazole and tetrazole fused quinazolinones in good yields. This methodology offers a convenient method for the synthesis of these important heterocyclic scaffolds in a highly atom economical process. On the mechanistic aspect weakly nucleophilic triazole and tetrazole moieties function as both directing as well as intramolecular nucleophiles. The catalytically active C–H activated intermediate dimeric Pd complex was isolated and characterized which on exposure to CO gas gave the corresponding tetrazole fused quinazolinone derivative. On the basis of isolation of the intermediate and observed kinetic isotope effects, a mechanism has been proposed for the C–H activated direct carbonylative annulation reaction.

Introduction

Since the seminal work of Heck, transition metal catalyzed carbonylation of organic halides and pseudo halides using carbon monoxide as a carbonyl source has become a powerful method for the synthesis of carboxylic acid and its derivatives and a wide variety of carbonylated heterocyclic compounds.[1] More recently the direct carbonylation of a C–H bond has resulted in the development of a more straightforward and atom economical approach.[2] The first direct oxidative carbonylation of arenes was introduced by Fujiwara in 1980 which involved an electrophilic attack on the arene by palladium(II).[3] Since then the focus has been on transition metal catalyzed regioselective arene C–H carbonylation.[4–7] In order to achieve selectivity various directing groups (DG) such as amides,[4] nitrogen containing heterocycles,[4c] carboxylic acids,[5] amidines[8e] and *tert*-amines[6] have been deployed, and often these directing groups also act as in-built nucleophiles.[9] Examples of directing groups in Pd(II) catalyzed intramolecular oxidative carbonylation of arenes are shown in Scheme 1. Derivatives of aminotriazole and aminotetrazole are important in medicinal chemistry.[10] Quinazolinone is an important scaffold found in nature and exhibits a wide range of biological activities including antibacterial, anti-inflammatory, antifungal and anti-cancer activities.[11]

While fused triazoloquinazolinone is well known and prevalent, the fused tetrazoloquinazolinone scaffold is still rare and both are potential candidates in medicinal chemistry due to their wide biological activities. Copper catalyzed oxidative annulation of arylacetamides is known to give fused quinazolinones.[11h] Triazole and tetrazole fused quinazolinones are gen-



Scheme 1 Intramolecular C–H carbonylation of arenes.

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Full Paper

Carbonylative Annulation

Highly Selective and Modular Synthesis of 3-Aryl-4-(arylethynyl)-2*H*-chromen-2-ones from 2-Iodoaryl 2-Arylacetates through a Carbonylative Sonogashira Coupling–Intramolecular Aldol Cascade Reaction

Attoor Chandrasekhar,[a] Venkatachalam Ramkumar,[a] and Sethuraman Sankararaman*[a]

Dedicated to Professor Dr. Henning Hopf on the occasion of his 75th birthday

Abstract: A modular method for the synthesis of 3-aryl-4-(arylethynyl)-2*H*-chromen-2-ones from 2-iodoaryl 2-arylacetates and arylacetylenes has been developed. The carbonylative Sonogashira coupling–intramolecular aldol casade reaction was carried out in the presence of $Pd(PPh_3)_2(Cl)_2$ as the catalyst. The one-pot approach that involves the in situ formation of the 2-iodoaryl 2-arylacetates from the corresponding 2-iodophenols and 2-arylacetyl chlorides followed by the palladium-catalyzed carbonylative annulation in the presence of the arylacetylene has also been described for the formation of the 3-aryl-4-(arylethynyl)-2*H*-chromen-2-ones.

Introduction

2*H*-Chromen-2-one (coumarin) and its derivatives are found in nature, especially in the plant kingdom.[1] They are an important class of compounds as they display a wide range of biological activities[2] and also have applications in materials chemistry as laser dyes, light-emitting diodes, and fluorescent probes.[3] The conventional synthesis of 2*H*-chromen-2-one by using a Perkin[4] or von Pechmann reaction[5] involves the condensations of substituted phenols with various carbonyl compounds. Modern transition-metal-mediated catalytic methods involve carbonylative annulation reactions that use carbon monoxide as a one-carbon source. Cobalt(III)-catalyzed carbonylative annulations of 2-alkenylphenols to give coumarin derivatives have been reported,[6] and this approach requires the synthesis of 2-alkenylphenols from the corresponding salicylaldehyde derivatives by a Wittig reaction. Palladium-catalyzed carbonylative annulations of internal alkynes and 2-iodophenols have been reported to give regioisomeric mixtures of 3,4-disubstituted coumarins from unsymmetrical internal alkynes.[7] In a related work, two examples of the synthesis of 3,4-disubstituted coumarins through a carbonylative annulation of 2-iodophenyl 3-alkenoate have been reported along with details of the formation of an aurone derivative as a byproduct.[8] Herein, we report a general and modular synthetic method for the synthesis of 3-aryl-4-(arylethynyl)-2*H*-chromen-2-ones from 2-iodoaryl 2-arylacetate and arylacetylene in the presence of $Pd(PPh_3)_2(Cl)_2$ as the catalyst under carbon monoxide (1 atm). An earlier report[9] of the synthesis of 4-arylethynyl-2*H*-chromen-2-ones used 4-hydroxycoumarin as the starting material. In that report, the tosylates of 4-hydroxycoumarins were generated in situ and subjected to palladium-catalyzed Sonogashira coupling reactions with terminal acetylenes.

Results and Discussion

The 2-iodoaryl 2-arylacetates **1a**–**g** were synthesized according to a literature method by employing the reaction between the corresponding 2-iodophenol and 2-arylacetyl chloride derivatives.[10] The carbonylative annulation reactions of **1a**–**g** with arylacetylenes **2a**–**e** were then carried out in toluene at 80 °C, as there was no reaction at room temperature (Scheme 1). These reactions were performed in the presence of $Pd(PPh_3)_2(Cl)_2$ (1 mol-%) as the catalyst and a balloon filled with CO (1 atm), and the progress of the reactions was monitored by TLC analysis. Under these conditions, the reactions proceeded cleanly and selectively towards the formation of coumarin derivatives **3a**–**v** and **3y** (Scheme 1) in high yields, and the corresponding Sonogashira coupling products, namely the 2-(arylethynyl)phenyl 2-arylacetates, were not observed. The absence of the Sonogashira coupling product suggests that the carbonylation reaction that follows the oxidative addition of Pd^0 across the C–I bond occurs much faster than the Sonogashira coupling reaction. Small amounts of 1,4-diarylbuta-1,3-diynes were obtained, presumably from the oxidative dimerization of the arylacetylenes.

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