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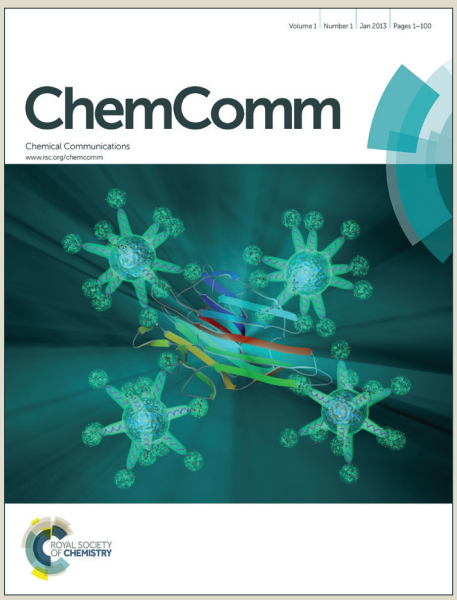

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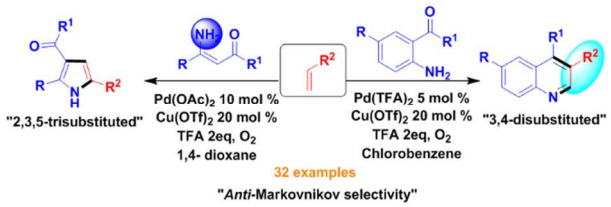

A novel strategy has been identified for the regioselective synthesis of 3,4-disubstituted quinolines and 2,3,5-trisubstituted pyrroles through *anti*-Markovnikov selectivity.

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Palladium(II)-catalysed regioselective synthesis of 3,4-disubstituted quinolines and 2,3,5-trisubstituted pyrroles from alkenes via *anti*-Markovnikov selectivity

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A novel strategy has been identified for the regioselective synthesis of 3,4-disubstituted quinoline and 2,3,5-trisubstituted pyrroles from simple alkenes via *anti*-Markovnikov selectivity under the palladium catalysis. The salient features are two different heterocycles synthesis, readily available starting materials, broad substrate scope, moderate to good yields and molecular oxygen as terminal oxidant.

Quinolines and pyrroles are privileged class of aromatic aza heterocycles because of their omnipresence in natural products,[1] medicinal chemistry[2a,b] and drug synthesis.[2c,d] In particular, 3,4-disubstituted quinoline and 2,3,5-trisubstituted pyrrole derivatives shown to possess interesting biological properties. (Figure 1).[3] The structural core of quinolines and

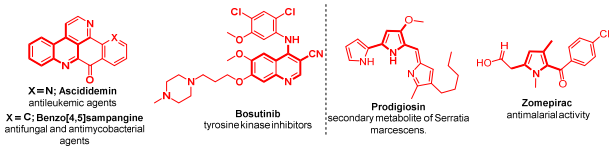
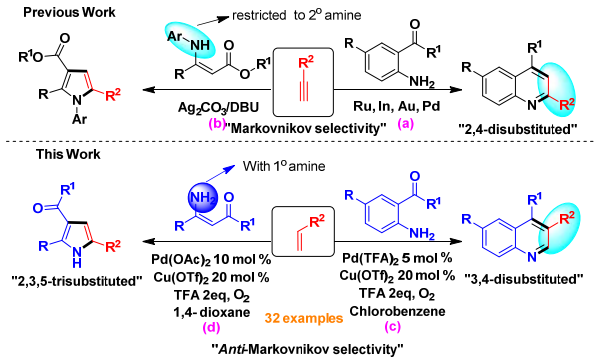


Figure 1. Biologically active quinolines and pyrroles

pyrroles can be synthesized by various classical methods[4] as well as from transition-metal catalysis.[5,6] Although numerous methods have been documented for the preparation of these aza heterocycles,[7] the regioselective, simple and expedient approaches for 3,4-disubstituted quinoline and 2,3,5-trisubstituted pyrroles still remain scarce and unexplored. Therefore, the identification of efficient catalytic system and readily available starting material for the regioselective generation of 3,4-disubstituted quinolines and 2,3,5-trisubstituted pyrroles continues to be a challenging task. Recently, *o*-acylanilines and enaminocarbonyls have been emerged as a versatile starting material for the synthesis of quinolines and pyrroles. Among them, Ru,[8a] In,[8b] Au[8c] and Pd[8d] catalysed reaction of alkyne with *o*-acylanilines has received significant attention. However, the obtained product was a regioselective 2,4-disubstituted quinolines or polysubstituted quinolines *via* a Markovnikov selectivity, which is a complementary approach to Friedlander synthesis. (Scheme 1a). On the other hand, Lei et al. developed the synthesis of 2,3,5-trisubstituted pyrroles from *β*-enaminoesters and terminal alkynes.[9a,b] But, the use of stoichiometric silver salts and the feasibility of reaction with *N*-aryl enaminoester limited the practicability of this method (Scheme 1b).

The above results motivated us to identify a new catalytic condition which involved aminopalladation and trapping of an *in situ* generated 2-aminoalkyl palladium into the carbonyl group as the key step for the synthesis of 3,4-disubstituted quinolines from *o*-acyl anilines and alkenes (Scheme 1c). Moreover, the synthesis of 2,3,5-trisubstituted pyrroles was achieved by a cascade consisting of C-C bond formation and amination as the key step from *β*-enaminoketones and vinyl arenes (Scheme 1d). To the best of our knowledge this is the first report to construct these azaheterocycles *via* *anti*-Markovnikov selectivity of simple alkenes.[10]



Scheme 1. Previous and this study on quinolines and pyrroles

Our initial investigation began by using commercially available 2-aminobenzophenone **1a** and styrene **2a** as substrate with various metal(II) salts, oxidants and additives (see ESI†).[11] The desired compound **3a** was obtained in 65%

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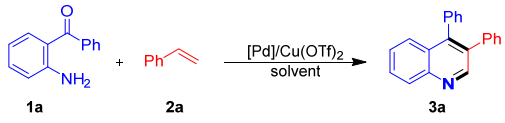
Electronic Supplementary Information (ESI) available: Experimental procedures and copies of ^{1}H and ^{13}C spectral data. See DOI: 10.1039/x0xx00000x

yield by using 5 mol % of $Pd(TFA)_2$, 1.0 equiv of $Cu(OTf)_2$, and 2.0 equiv of trifluoroacetic acid (TFA) in the presence of 1,4-dioxane at 110 °C for 16h (entry 1). Next, the choice of solvent was studied (entries 2-8) and the best result was obtained using chlorobenzene (entry 8). Interestingly, the target compound **3a** was generated in 87% yield by reducing the amount of $Cu(OTf)_2$ to a catalytic quantity (20 mol %) in the presence of O_2 as a terminal oxidant (entry 9). The reaction did not generate the desired compound **3a** in the absence of $Cu(OTf)_2$ (entry 10) as well as with $Cu(OTf)_2/O_2$ (entry 11). The reaction was unsuccessful in the absence of TFA (entry 12) and also in the basic condition using acetate salt (entry 13). By replacing the $Pd(TFA)_2$/Chlorobenzene with $Pd(OAc)_2$/1,4-dioxane also failed to create compound **3a** (entry 14). Finally, the equivalent studies of $Pd(TFA)_2$ and $Cu(OTf)_2$ (entries 15-18) revealed that 5 mol% of $Pd(TFA)_2$ and 20 mol % of $Cu(OTf)_2$ as the best combination (entry 9).

Table 1. Optimization of the reaction conditions[a]



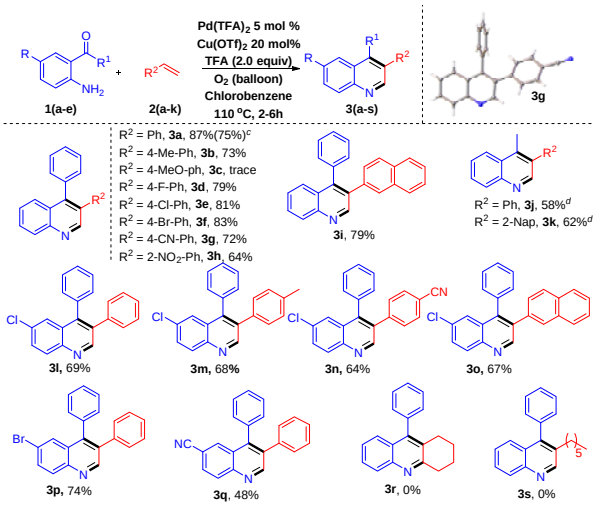
1a 2a 3a

Entry	Catalyst (x mol %)	Oxidant (y mmol)	Solvent[h]	Yield (%)[b]
1	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	1,4-dioxane	65
2	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	DMSO	12
3	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	DMF	27
4[c]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	CH_3CN	14
5[c]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	1,2-DCE	39
6[d]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	THF	68
7[e]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	Toluene	82
8[e]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.5)	PhCl	89
9[e,f]	**$Pd(TFA)_2$ (5)**	**$Cu(OTf)_2$ (0.1)**	**PhCl**	**87**
10[e,f]	$Pd(TFA)_2$ (5)	---	PhCl	ND
11[e]	$Pd(TFA)_2$ (5)	---	PhCl	NR
12[g]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.1)	PhCl	ND
13[i]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.1)	PhCl	NR
14[e,f]	$Pd(OAc)_2$ (10)	$Cu(OTf)_2$ (0.1)	1,4-dioxane	Trace
15[f,j]	$Pd(TFA)_2$ (2.5)	$Cu(OTf)_2$ (0.1)	PhCl	75
16[e,f]	$Pd(TFA)_2$ (10)	$Cu(OTf)_2$ (0.1)	PhCl	85
17[f,j]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.05)	PhCl	85
18[e,f]	$Pd(TFA)_2$ (5)	$Cu(OTf)_2$ (0.15)	PhCl	70

[a] All reactions were carried out using **1a** (0.50 mmol), **2a** (0.75 mmol), catalyst (x mol %), oxidant (y mmol), TFA (1.016 mmol) and solvent (2.0 mL) for 16h at 110 °C unless otherwise noted. [b] Isolated yields. [c] At 80 °C. [d] At 65 °C. [e] For 4h. [f] O_2 balloon was used. [g] Without TFA. [h] Chlorobenzene (PhCl). [i] NaOAc (1.0 mmol) was used instead of TFA. [j] For 12 h. NR = No reaction. ND = Not detected.

As shown in Table 2, the scope and limitations for the formation of quinolines **3a**-**3s** was investigated using systematic variation *o*-acyl anilines (**1a**-**1e**) and alkenes (**2a**-**2k**). Pleasingly the reaction performed on a gram scale underwent smooth conversion to generate compound **3a** in 75 % yield. A series of substituents on vinyl arenes including *p-Me*, *p-F*, *p-Cl*, *p-Br*, *p-CN* and *o-NO*$_2$ were tolerated and the corresponding 3,4-disubstituted quinoline derivatives **3a**, **3b**, **3d**-**3h** were obtained in moderate to good yields except *p-MeO* derivative **3c** due to the strong electron donating nature. The reaction also worked well for the fused systems such as 2-vinyl naphthalene to generate compound **3i** with a 79% yield. The feasibility of the reaction was evaluated using 2-aminoacetophenone **1b**, but the desired compounds **3j** and **3k** was obtained in very low yields. Hence by changing catalyst to $Pd(OAc)_2/Cu(OAc)_2$ system (Table 2, entry **3j** and **3k**), the yield was substantially improved. Then, the scope of R- group on the 2-aminobenzophenone was tested using *5-Cl*, *5-Br* and *5-CN* (**1c**-**1e**). The reaction progressed well in all the cases to generate the target compound **3l**-**q**. The obtained compound **3p** can be used for various metal catalysed transformations. However, aliphatic alkenes such as cyclohexene and 1-octene, did not work under these conditions to get compounds **3r** and **3s**. The probable reason could be the low reactivity of aliphatic alkenes.

Table 2. Substrate scope of *o*-acyl anilines and alkenes[a,b]

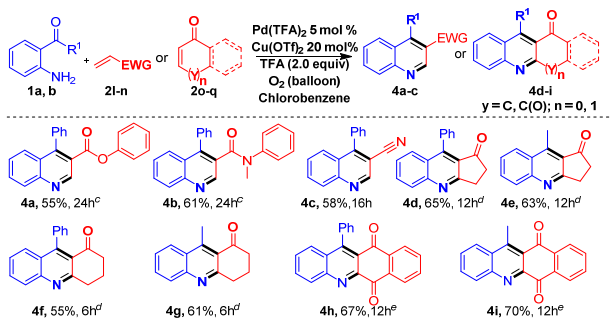


[a] Reaction conditions: Compound **1a**-**e** (0.50 mmol), alkenes **2a**-**k** (0.75 mmol), $Pd(TFA)_2$ (5 mol %), $Cu(OTf)_2$ (20 mol %), TFA (1.0 mmol) in chlorobenzene (2.0 mL) under a O_2 balloon for 2-6 h at 110 °C. [b] Isolated yields. [c] Reaction performed on 1.0 g scale of **1a**. [d] $Pd(OAc)_2$ 5 mol %, $Cu(OAc)_2$ 1.0 mmol was used in 1,4-dioxane for 16h at 110 °C.

In the light of success with styrene derivatives, we next envisioned the synthesis of quinolines with various functional groups at the 3-position as shown in Table 3. Interestingly, quinolines functionalized with ester **4a**, amide **4b** and nitrile **4c** were obtained in moderate yields. These compounds can be potentially utilized for various synthetic organic transformations. Further, we used 1-cyclopentenone **2o**/1-cyclohexenone **2p** and both of them gave the desired compounds **4d**-**4g**. The reaction also went smoothly using napthaquinone **2q** to furnish compounds **4h** and **4i**.[10b] Notably, compound **4i** is the final precursor for the synthesis of benzo[4,5]sampangine, which is a used as an antifungal and antimycobacterial agent.[3b] The regioselectivity was confirmed with the help of X-ray crystal structure and also through downfield shifted H2 in all the quinolines by ^{1}H NMR analysis.

To further extend the scope of the synthesis for pyrrole

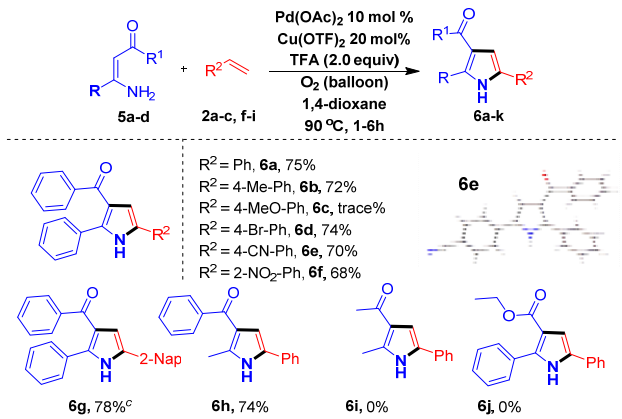
Table 3. Substrate scope of 3-functionalized quinolines and their fused derivatives[a,b]



[a] Reaction conditions: Compound **1a**,**b** (0.50 mmol), alkenes **2l-q** (0.75 mmol), $Pd(TFA)_2$ (5 mol %), $Cu(OTf)_2$ (20 mol %), TFA (1.0 mmol) in chlorobenzene (2.0 mL) under a O_2 balloon at 110 °C unless otherwise noted. [b] Isolated yield. [c] 1.0 mmol of $Cu(OTf)_2$ was used without O_2 balloon. [d] At 60 °C. [e] 50 mol % of $Cu(OTf)_2$.

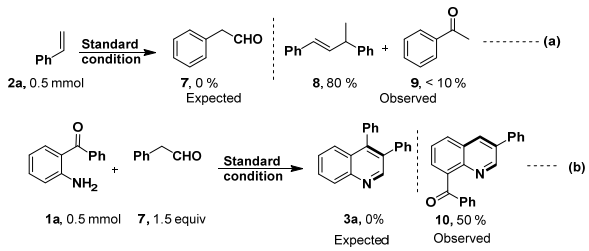
derivatives, we have chosen enaminones **5a** and reacted with styrene **2a**, under the optimized conditions and the desired pyrrole **6a** was formed albeit in a low yield (19%). Replacing $Pd(TFA)_2$/chlorobenzene with $Pd(OAc)_2$/1,4-dioxane gave the compound **6a** in a respectable yield (Table 4).[11] Further, the scope of the reaction was established with various styrene as well as enaminones derivatives and all of them worked well to generate the corresponding pyrrole derivatives (**6b**,**6d**-**6h**)except the *p-MeO* due to the strong electron donating nature. Unfortunately, the reaction also failed to produce compounds **6i** and **6j** under standard condition. The structures of the compounds **3g**, **4a**, **4c** and **6e** were confirmed by X-ray analysis.[12] Recently, Chen and co-workers developed copper-mediated cross-coupling–cyclization–oxidation of alkenes, anilines and β-ketoesters for the synthesis of polysubstituted pyrroles via radical mechanism. However, the reaction is restricted to secondary β-enaminoesters. Thus, when we performed our reaction using their condition, no product formation was observed.[13a]

Table 4. Substrate scope of 2,3,5- trisubstituted pyrroles[a,b]



[a] Reaction conditions: Compound **5a-d** (0.50 mmol), vinyl arenes **2a-c, f-i** (0.75 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OTf)_2$ (20 mol %), TFA (1.0 mmol) in 1,4-dioxane (2.0 mL) under O_2 balloon for 1-6 h at 90 °C. [b] Isolated yields. [c] 2-Naphthyl (2-Nap).

To gain some preliminary understanding on the mechanism, control experiments were carried out under standard conditions (Scheme 2).[11] The reaction of compound **2a** under optimized condition gave the dimerized product **8** in 80% and trace amount of Wacker oxidation product **9**, but not the expected aldehyde selective Wacker oxidation product **7**[13b] (Scheme 2a).This result eliminated the formation of phenyl acetaldehyde intermediate **7**. Next, 2-aminobenzophenone **1a** and phenyl acetaldehyde **7** were treated under standard protocol, but the desired compound **3a** was not formed, instead phenyl(3-phenylquinolin-8-yl)methanone **10** was isolated in 50 % yield (Scheme 2b). A similar observation was reported by Huang et al. using aniline and phenyl acetaldehyde **7** in the presence of CuBr/TfOH and they proposed that the reaction proceeds via enamine intermediate.[5f] These results indicated that our present protocol might involve trapping of *in situ* generated 2-amino alkyl palladium with ketone and ruled out the formation of enamine intermediate via β-hydride elimination.

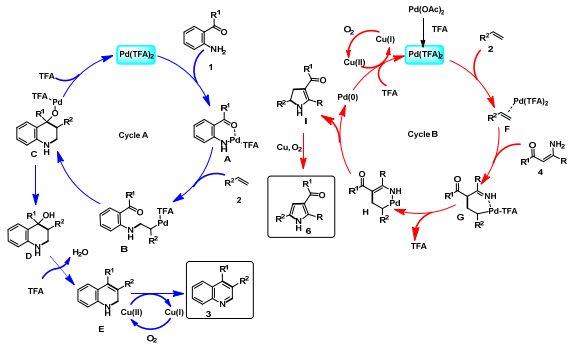


Scheme 2. Preliminary mechanistic studies

A plausible mechanism was proposed in Scheme 3, and is based on our obtained results. The initial step of cycle A begins with a carbonyl group directed palladation of the N-H bond to form intermediate **A**.[8d] The intermediate **A** is merely a plausible yet not observed structure. Next, intermolecular addition of the *N*-palladium bond across the terminal alkenes gave the thermodynamically favoured *anti*-Markovnikov regioselective 2-amino alkyl palladium intermediate B.[14] The rationalism for this selectivity over the kinetically favoured Markovnikov product could arise due to the slow deprotonation of N-H under the acidic reaction conditions.[14a] Furthermore, the intramolecular nucleophilic addition of **B** to the carbonyl group produced intermediate **C**.[8d,15] Protolysis of the palladium alkoxide **C** gave alcohol **D** and the active Pd(II) was regenerated for the next catalytic cycle. Finally, dehydration of **D** followed by oxidation of **E** under copper (II) and molecular oxygen as a terminal oxidant afforded the quinoline derivatives **3**.[11]

On the other hand, the coordination of Pd(II) with alkenes **2** gave the intermediate **F** (Cycle B).[16a] Intermolecular C-C bond formation of enaminones across the terminal alkenes produced the regioselective *anti*-Markovnikov σ-alkyl palladium intermediate **G**. Further, the intermediate **G** underwent amination to generate intermediate **H**. Finally, reductive elimination followed by oxidation produced the pyrrole derivatives **6**. Alternatively, β-hydride elimination of **G** would generate alkene intermediate and active Pd(II) will be regenerated in the presence of oxidant. Then, the intramolecular 5-*endo*–*trig* annulation[16b] followed by β-

hydride elimination also produce the target pyrrole **6**.[16c] (See ESI†).[11]



Scheme 3. Proposed reaction pathway.

In conclusion we have presented a new catalytic system for the synthesis of 3,4-disubstituted quinolines and 2,3,5-trisubstituted pyrroles from *o*-acylanilines/β-enaminones with alkenes. The mechanistic studies suggested that the *in situ* generated 2-amino alkyl palladium intermediate trapping with the carbonyl group was the key step for the formation of 3,4-disubstituted quinolines. For the first time using these readily available substrates, the reaction proceeded with a highly regioselective *anti*-Markovnikov alkene selectivity. Further mechanistic studies for pyrrole formation is under progress.

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The authors acknowledge the funding from ministry of science and technology (MOST), Taiwan. We also thank the Centre for Research Resources and Development of Kaohsiung Medical University for providing 400 MHz NMR support.

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10 (*a*) During the course of completion of this research, we found that Li et al. reported the copper-catalysed intermolecular Ullmann-type C-N coupling/enamine condensation with *ortho*-acylanilines and alkenyl iodides for the synthesis of quinolines. But the use of halo-functionalized alkenes reduces the substrate scope and practicality of this approach. See reference (5h); (*b*) We can able to see the β-hydride elimination intermediate by TLC

11 For optimization studies for the synthesis of compound **3a** and **6a**, control experimental studies and alternative mechanism, (see the ESI†).

12 CCDC 1063744 (**3g**), 1063745 (**4a**), 1063746 (**4c**) and 1063747 (**6e**).

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