

Article

Practical Pd(TFA)₂-Catalyzed Aerobic [4+1] Annulation for the Synthesis of Pyrroles via “One-Pot” Cascade Reactions

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Abstract: The Pd(TFA)₂-catalyzed [4+1] annulation of chained or cyclic α -alkenyl-dicarbonyl compounds and unprotected primary amines for “one-pot” synthesis of pyrroles is reported here. Enamination and amino-alkene were involved in this practical and efficient tandem reaction. The annulation products were isolated in moderate to excellent yields with O₂ as the terminal oxidant under mild conditions. In addition, this method was applied to synthesize highly regioselective aminomethylated and di(1H-pyrrol-3-yl)methane products.

Keywords: Pd(TFA)₂; [4+1] annulation; α -alkenyl-dicarbonyl compounds; unprotected primary amines; one-pot; tandem reaction; regio-selective

1. Introduction

Pyrrole is one of the most significant *N*-containing heterocycles, and is the component of numerous biologically active molecules [1–3], natural products [4–6] and functional materials [7–9]. For example, atorvastatin **A** [10,11], which is one of the world’s best-selling drugs, was first introduced to the market in 1997 by Pfizer as an effective HMG-CoA reductase inhibitor for lowering blood cholesterol. Prodigiosin **B** [12,13], isolated from *Serratia marcescens* has been continuously investigated for medically relevant properties including antimalarial activity and anticancer activity. Corrole **C** [14,15] and its derivatives have been used to detect environmental pollutants or biologically important species. In addition, 6,7-dihydro-1*H*-indol-4(5*H*)-one and their derivatives also play a more and more important role because of their extensive application as versatile building blocks in organic synthesis. For instance, HSP90 was a therapeutic target for cancer treatment, and compound **D** [16] possessed a modest level of HSP90 α/β isoform selectivity. *R*-Ondansetron **E** [17] is a synthetic drug used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery. Compound **F** [18] is an antiproliferative compound that has been reported containing antitumor activity (Figure 1).

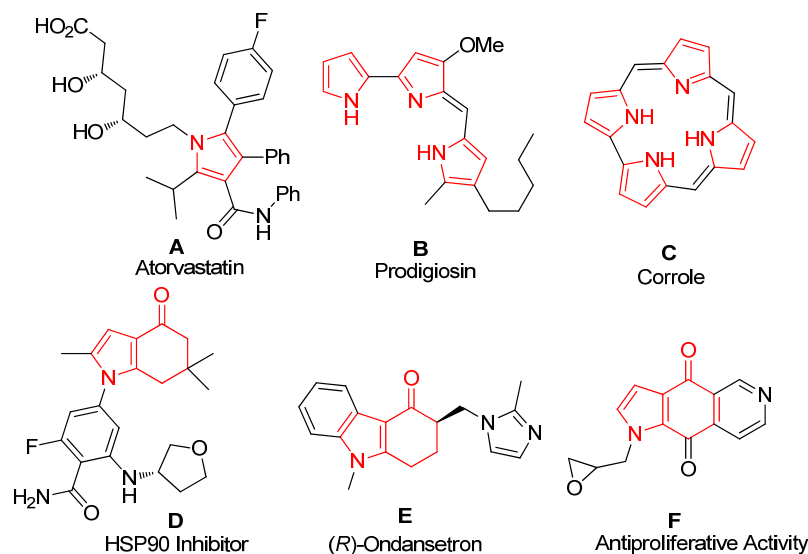


Figure 1. Bioactive compounds containing pyrroles.

There has been a long-standing interest in the development of efficient methods for the preparation of highly substituted pyrroles due to their widely biological activities. The classical synthetic methods include Barton–Zard [19], Paal–Knorr [20,21], and Hantzsch reactions [22,23].

However, they suffer from several drawbacks such as harsh reaction conditions, sophisticated operations, and poor availability of the starting materials and functional group tolerance [24]. In recent years, efficient synthetic approaches to construct organic frameworks containing pyrroles have been developed [25–35]. On the other hand, the transition-metal-catalyzed sp^2 C–H amination reaction is one of the most demanding procedures to form C–N bonds [36,37]. In recent years, various late transition metal catalysts such as Pd [38–41], Ru [42], Rh [43], Ir [44], and Cu [45] have been applied in sp^2 C–H bond amination. Within this methodology, Pd-catalyzed intramolecular aza-Wacker-type oxidative reactions represent one crucial route to produce a range of 5-membered N-containing heterocycles [46–51]. However, intermolecular aza-Wacker-type oxidative amination has been rarely reported and protection of the amine nitrogen is often required in the reaction because palladium species would be deactivated via coordination of the unprotected amine to the metal center in most cases [41,52–54]. Furthermore, benzoquinone, $Cu(OAc)_2$ and other inorganic salt have often been used in Wacker oxidative reactions as oxidative reagents [55–57]. However, large numbers of organic oxidants or inorganic salts have not been able to meet the requirements of green chemistry and sustainable development. Aiming to deal with these problems, we described the first palladium-catalyzed intermolecular aza-Wacker-type cyclization in 2013, which gave highly substituted pyrroles from 2-alkenyl-1,3-dicarbonyl compounds with unprotected primary amines in a “one-pot” reaction [58]. According to the deuteration studies of the annulation reaction (see supplementary information), a probable mechanism is proposed as shown in Figure 2. Enamine **3** takes place with loss of TFA to generate the Pd-alkyl intermediate **II**. Then **II** undergoes β -hydride elimination and Pd–H reinsertion to form **IV**. The second β -hydride elimination gives pyrrole **4**. The Pd(0) is then oxidized by O_2 to regenerate catalyst Pd(II).

To continue our research on C–N bond forming reactions [59–65], we sought to broaden dicarbonyl scope and study the application of the cycloaddition products found as key intermediates in the synthesis of biologically active compounds. Herein, we present a full account of our recent work on the Pd-catalyzed [4+1] annulation reaction.

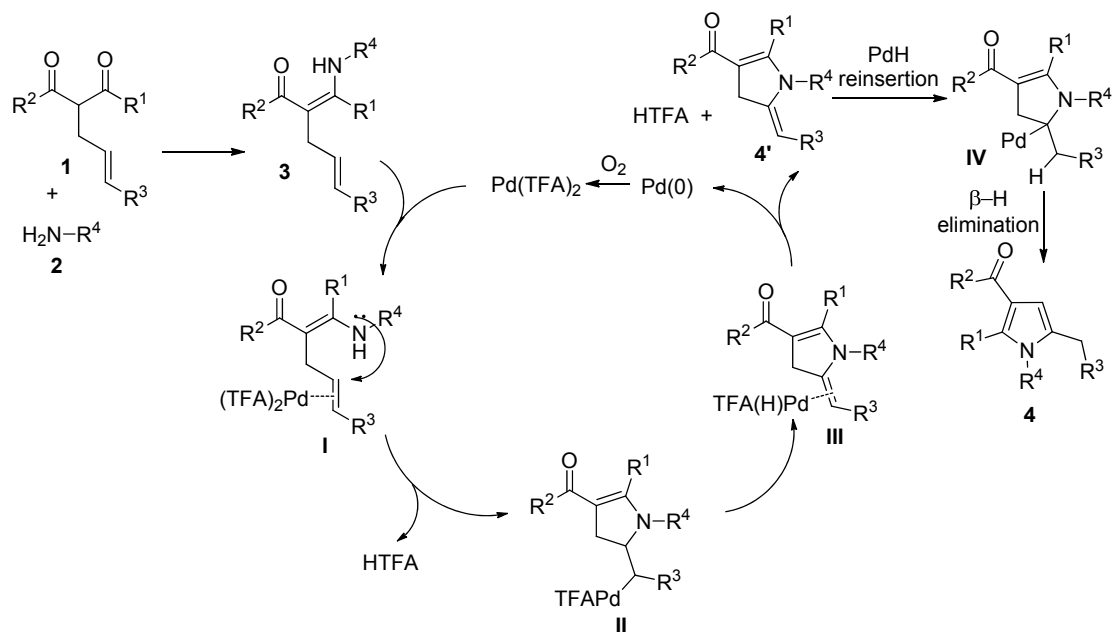


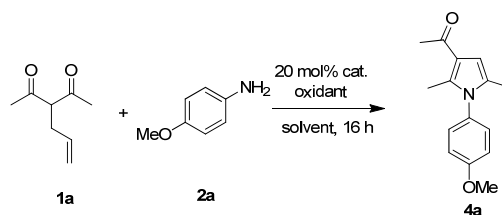
Figure 2. Proposed mechanism of Pd(TFA)₂-catalyzed [4+1] annulation.

2. Results and Discussion

2.1. Optimized Synthesis of 4a

In the initial attempt on the formation of pyrroles, when a mixture of **1a** and **2a** in toluene was heated at 80 °C, enaminone derivative **3a** was formed. The reaction mixture was then directly treated with a catalytic amount of Pd(OAc)₂ (20 mol %) and was stirred at 60 °C for 16 h. The reaction formed the desired product pyrrole **4a** in 48% yield.

Encouraged by the outcome, the solution of **1a** (2.0 eq) and **2a** (1.0 eq) in toluene was stirred at 60 °C for 16 h in the presence of Pd(OAc)₂ (20 mol %). The desired product **4a** was obtained in 45% yield (Table 1, entry 1). Next, the reaction conditions were optimized to improve reaction yields (Table 1). The solvent screening revealed that polar aprotic solvents such as dimethylacetamide (DMA), dimethyl sulphoxide (DMSO), and dimethylformamide (DMF) afforded the products in poor yields (entries 2–4). 1,2-Dichloroethane (DCE) gave a slightly higher yield than CH₃CN and tetrahydrofuran (THF) (entries 5–7). The results showed that toluene was the most suitable solvent for the reaction. When different oxidants were screened, it was found that air, Cu(OAc)₂, and AgOAc were less effective than O₂ (entries 8–11). What is more, when Pd(TFA)₂ was used as the catalyst, the yield of product **4a** was improved to 82% (entry 12). Then other Pd species were screened, and PdCl₂, PdCl₂(PPh₃)₂, PdCl(CH₃CN)₂, and Pd(PPh₃)₄ were found to afford the products in poor reaction yields (entries 13–16). Additionally, when the reaction was carried out for 1.5 h, a slightly higher yield was achieved (86%, entry 17). Lower catalyst loading needed longer reaction time without any yield sacrifice (entries 18 and 19).

Table 1. Optimized Synthesis of 4a^a.

Entry	Solvent	Catalyst	Oxidant	Yield ^b (%)
1	toluene	Pd(OAc) ₂	air	45
2	DMA	Pd(OAc) ₂	air	18
3	DMSO	Pd(OAc) ₂	air	12
4	DMF	Pd(OAc) ₂	air	32
5	DCE	Pd(OAc) ₂	air	40
6	CH ₃ CN	Pd(OAc) ₂	air	23
7	THF	Pd(OAc) ₂	air	25
8	xylenes	Pd(OAc) ₂	air	50
9	xylenes	Pd(OAc) ₂	Cu(OAc) ₂	21
10	xylenes	Pd(OAc) ₂	AgOAc	trace
11	xylenes	Pd(OAc) ₂	O ₂	58
12	xylenes	Pd(TFA) ₂	O ₂	82
13	xylenes	PdCl ₂	O ₂	28
14	xylenes	PdCl ₂ (PPh ₃) ₂	O ₂	14
15	xylenes	PdCl ₂ (CH ₃ CN) ₂	O ₂	trace
16 ^c	xylenes	Pd(PPh ₃) ₄	O ₂	17
17 ^d	toluene	Pd(TFA) ₂	O ₂	86
18 ^e	toluene	Pd(TFA) ₂	O ₂	85
19 ^f	toluene	Pd(TFA) ₂	O ₂	88

^a A solution of **1a** (1.2 mmol) and **2a** (0.6 mmol) with catalyst (0.03 mmol) in the solvent (2 mL) was stirred at 60 °C for 16 h. ^b Isolated yield. ^c The reaction time is 2 h. ^d The reaction time is 1.5 h. ^e 10 mol % catalyst was used with the reaction time of 9 h. ^f 5 mol % catalyst was used with the reaction time of 16 h.

2.2. One-Pot Synthesis of 4

With the optimal reaction conditions in hand, we then examined the substrate scope of the Pd(TFA)₂-catalyzed tandem process for the formation of pyrroles **4**. As shown in Figure 3, almost all of the tested combinations produced the desired pyrroles **4** in good to excellent isolated yields. Generally, electron-donating groups on the benzene ring have a positive effect on the yield due to enhancement of the nucleophilicity of the nitrogen atom. The substitution pattern of the methoxy group on the phenyl ring of the anilines has a slight impact on the yields (**4a–4c**) despite a small drop due to the steric effect. The reaction of aniline also proceeds smoothly with 77% yield (**4d**). Furthermore, the anilines bearing other electron-donating groups on the phenyl ring are also suitable for this protocol (**4e–4g**). Further, the substrates bearing two substituents on the phenyl ring such as 2-naphthalenamine, 3,4-dimethylaniline, and 4-methoxy-2-methylaniline are also compatible, as illustrated by the formation of the pyrrole products **4h–4j** in good yields (74%–85%).

However, the limitation of the process is also recognized; the anilines with electron-withdrawing groups on the phenyl ring give poor yields under this reaction condition (**4k** and **4l**, 40%–50%). Besides, we noted that the aliphatic amines could also engage in the process to afford the corresponding pyrroles **4m** and **4n** with high yields. Probing the diketone substrates implies that more hindered diketone ($R^1 = R^2 = \text{Et}$) appears to be a good candidate for this tandem reaction (**4o**). Moreover, the variation of R^2 functionalities on **1** such as Ph and OEt groups lead to the structurally diverse pyrroles **4p–4r** in good yields. Finally, we examined the challenging non-terminal alkene substrates. Pyrrole **4s** was formed ($R^3 = \text{Ph}$) in 65% yield.

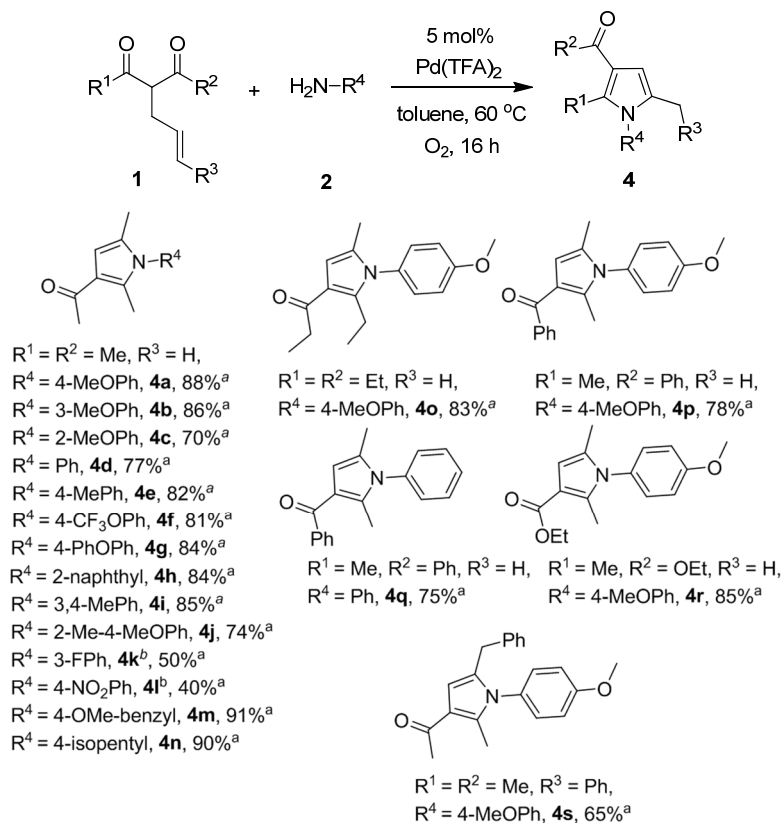


Figure 3. Scope of Pd(TFA)₂-catalyzed synthesis of pyrroles **4**. ^a Isolated yield. ^b 20 mol % catalyst was used.

2.3. One-Pot Synthesis of **6**

To further expand the scope of the reaction, cyclic diketones **5** and primary amine **2** were investigated (Figure 4). When the reaction was carried out under the standard reaction conditions, the yield of desired product was only 38%. However, we were pleased to find that the reaction yield was improved to 71% in 9 h by increasing the catalyst's loading to 20 mol % (**6a**). Then, other substrates were examined under the same reaction condition. Both electron-withdrawing and electron-donating substituents on the aniline were tolerated in this reaction. The reaction gave slightly lower yields when *R*³ was *para*-MeOPh (**6b**, 64%). However, when *R*³ was *para*-MePh or *para*-BrPh, the products were formed in moderate yields (**6c** and **6d**). When *meta*-CF₃Ph was tested, the reaction worked with a useful yield (**6e**). Furthermore, the reaction of aniline, bearing *ortho*-ClPh, afforded the corresponding product in generally good yield (**6f**). It is worth mentioning that the reactions proceeded smoothly when the substituted group of the 5-position of cyclic diketone was methyl or dimethyl (**6g** and **6h**). However, the reaction was not tolerable for **5i** with phenyl at the 5-position of cyclic diketone (**6i**).

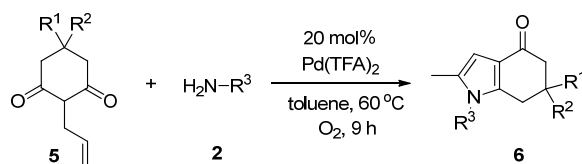


Figure 4. Cont.

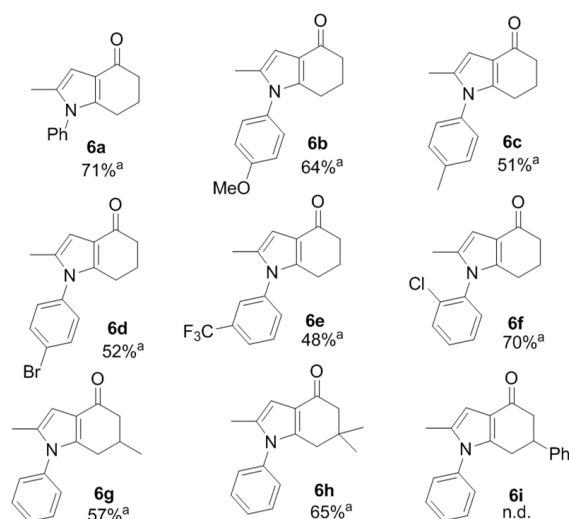


Figure 4. Scope of Pd(TFA)₂-catalyzed synthesis of pyrroles **6**. ^a Isolated yield.

2.4. Synthesis of Aminomethylated and Di(1*H*-Pyrrol-3-yl)methane Products

1-Phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one and its derivatives are important intermediates for the synthesis of bioactive compounds. The Cirrincione group reported the synthesis of **7a**, which has photochemotherapeutic activity toward cultured human tumor cells [66]. Martínez and coworkers reported that **7d** has cytotoxic activity as DNA intercalator [67] and **7h** could work as cyclin-dependent kinases (CDK) inhibitor [68]. These bioactive compounds were synthesized respectively from **6a**, **6d**, and **6h** (Figure 5).

However, the current studies on **6** were focused on modifying the α position of the cyclic ketone. It was found that C-3 of pyrrole was more active than the α position of cycloketone in our study. An aminomethylated product was synthesized smoothly from product **6a** through the acetic acid-promoted Mannich reaction of three-component, (CH₂O)_{*n*}, 1-methylpiperazine and **6a**. Interestingly, the desired β -aminocarbonyl compound was not formed, and the reaction furnished aminomethylated product **8a** at C-3 of pyrrole in 82% yield. In addition, when **6a** reacted in the presence of (CH₂O)_{*n*} and HCl instead of 1-methylpiperazine in dioxane, the unexpected di(1*H*-pyrrol-3-yl)methane derivative **9a** was obtained in 78% yield (Figure 6).

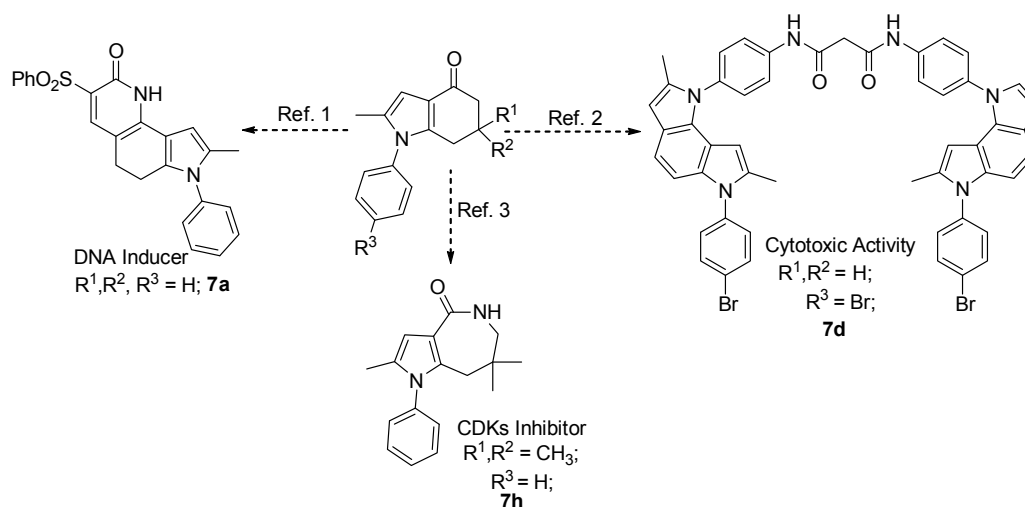


Figure 5. Synthetic transformation of **6** according to the literature.

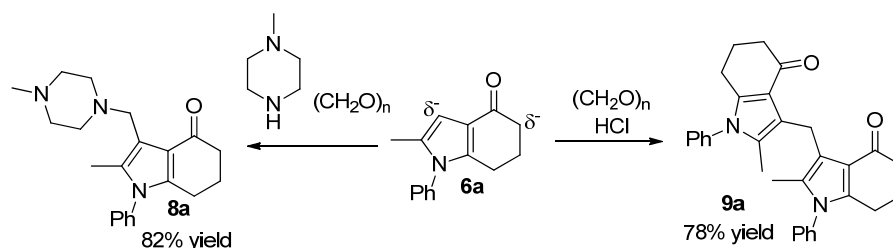


Figure 6. Further transformation of 6a.

3. Experimental Section

3.1. One-Pot Synthesis of 4

All the reactions were carried out under an aerobic atmosphere. To a solution of α -alkenyl-dicarbonyl **1** (1.2 mmol) and amines **2** (0.6 mmol) in dry toluene (2 mL), Pd(TFA)₂ (0.03 mmol, 0.05 eq) was added. The reaction mixture with an O₂ balloon was stirred for 16 h at 60 °C. The mixture was filtered through celite, washed with methanol (30 mL), the filtrate concentrated, and the residue was purified by column chromatography, hexane/EtOAc (*v/v*, 20/1 then 10/1) as eluent, giving the desired pyrrole products **4** as an oil.

3.2. Synthesis of 6

All the reactions were carried out under an aerobic atmosphere. To a solution of α -alkenyl diketones **5** (1.2 mmol), and amines **2** (0.6 mmol) in dry toluene (2 mL), Pd(TFA)₂ (0.12 mmol, 0.2 eq) was added. The reaction mixture with an O₂ balloon was stirred for 9 h at 60 °C. The mixture was filtered through celite, washed with methanol (30 mL), the filtrate concentrated, and the residue was purified by column chromatography, hexane/EtOAc (*v/v*, 10/1 then 4/1) as eluent, giving the desired pyrrole products **6**.

3.3. Synthesis of 8a and 9a

To a suspension of compound **6a** (45 mg, 0.2 mmol, 1.0 eq) and polyformaldehyde (18 mg, 0.6 mmol, 3.0 eq) in glacial acetic acid (0.4 mL), *N*-methyl piperazine (60 mg, 0.6 mmol, 3.0 eq) was added at 25 °C. The mixture was stirred at 25 °C overnight. Water (5 mL) was added, and the pH was then adjusted to pH 8–9 with ammonium hydroxide. The reaction mixture was extracted with dichloromethane. The combined organic phases were washed with water (5 mL \times 3), dried over MgSO₄, followed by concentration under vacuum, then washed with *n*-hexane, affording **8a** as a pink solid (55 mg, yield 82%).

A solution of **6a** (45 mg, 0.2 mmol, 1.0 eq) in dioxane (1.0 mL), polyformaldehyde (18 mg, 0.6 mmol, 3.0 eq) and HCl (conc., 1 mL) was added. The mixture was stirred at 25 °C for 2 h. The solution was concentrated, the crude product was purified by column chromatography on silica gel (PE/EA = 5/1) to give the desired compound **9a** as a light yellow powder (36 mg, yield 78%).

4. Conclusions

In summary, we have developed a Pd(TFA)₂-catalyzed [4+1] annulation reaction of chained or cyclic α -alkenyl-dicarbonyl compounds with unprotected primary amines. The reaction forms highly substituted pyrroles in a cascade fashion in moderate to excellent yields, and a diverse range of substrates are suitable. The reaction provides a new “one-pot” method for the synthesis of pyrroles. The process uses simple 2-alkenyl-dicarbonyl compounds and primary amines to prepare highly substituted pyrroles in a cascade fashion in moderate to excellent yields for a diverse range of substrates. It is worth noting that unexpected highly regio-selective aminomethylated and di(1H-pyrrol-3-yl)methane products were formed from the annulation products.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/6/11/169/s1.

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Author Contributions: Yang Yu and Zhiguo Mang performed the experiments of the cyclic α -alkenyl-dicarbonyl compounds and analyzed the data. Wei Yang contributed to the other experiments. Yang Yu wrote the first draft of the manuscript that was then improved by Hao Li and Wei Wang.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bellina, F.; Rossi, R. Synthesis and biological activity of pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions. *Tetrahedron* **2006**, *62*, 7213–7256. [[CrossRef](#)]
2. Syamaiah, K.; Mallikarjuna Reddy, G.; Padmavathi, V.; Padaja, A. Synthesis and antimicrobial activity of some new amido/sulfonamido-linked 3,4-disubstituted pyrroles. *Med. Chem. Res.* **2014**, *23*, 3287–3297. [[CrossRef](#)]
3. Yoshimura, H.; Kikuchi, K.; Hibi, S.; Tagami, K.; Satoh, T.; Yamauchi, T.; Ishibahi, A.; Tai, K.; Hida, T.; Tokuhara, N.; et al. Discovery of novel and potent retinoic acid receptor α agonists: Syntheses and evaluation of benzofuranyl-pyrrole and benzothiophenyl-pyrrole derivatives. *J. Med. Chem.* **2000**, *43*, 2929–2937. [[CrossRef](#)] [[PubMed](#)]
4. Clive, D.L.J.; Cheng, P. The marinopyrroles. *Tetrahedron* **2013**, *69*, 5067–5078. [[CrossRef](#)]
5. Rudi, A.; Evan, T.; Akin, M.; Kashman, Y. Polycitron B and Prepolycitron A: Two novel alkaloids from the Marine Ascidian Polycitron africanus. *J. Nat. Prod.* **2000**, *63*, 832–833. [[CrossRef](#)] [[PubMed](#)]
6. Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. Lamellarin D: A novel potent inhibitor of topoisomerase I. *Cancer Res.* **2003**, *63*, 7392–7399. [[PubMed](#)]
7. Gryko, D.T.; Gryko, D.; Lee, C.H. 5-Substituted dipyrroles: Synthesis and reactivity. *Chem. Soc. Rev.* **2012**, *41*, 3780–3789. [[CrossRef](#)] [[PubMed](#)]
8. Sadki, S.; Schottland, P.; Brodic, N.; Sabouraud, G. The mechanisms of pyrrole electropolymerization. *Chem. Soc. Rev.* **2000**, *29*, 283–293.
9. Haketa, Y.; Tamura, Y.; Yasuda, N.; Maeda, H. Dipyrrolylpyrimidines as anion-responsive π -electronic systems. *Org. Biomol. Chem.* **2016**, *14*, 8035–8038. [[CrossRef](#)] [[PubMed](#)]
10. Chen, X.; Xiong, F.; Chen, W.; He, Q.; Chen, F. Asymmetric synthesis of the HMG-CoA reductase inhibitor atorvastatin calcium: An organocatalytic anhydride desymmetrization and cyanide-free side chain elongation approach. *J. Org. Chem.* **2014**, *79*, 2723–2728. [[CrossRef](#)] [[PubMed](#)]
11. Wang, W.D.; Gao, X.; Strohmeier, M.; Wang, W.; Bai, S.; Dybowski, C. Solid-state NMR studies of form I of atorvastatin calcium. *J. Phys. Chem. B* **2012**, *116*, 3641–3649. [[CrossRef](#)] [[PubMed](#)]
12. Papireddy, K.; Smilkstein, M.; Kelly, J.X.; Salem, S.M.; Alhamadsheh, M.; Haynes, S.W.; Challis, G.L.; Reynolds, K.A. Antimalarial Activity of Natural and Synthetic Prodiginines. *J. Med. Chem.* **2011**, *54*, 5296–5306. [[CrossRef](#)] [[PubMed](#)]
13. Hu, D.X.; Withall, M.D.; Challis, G.L.; Thomson, R.J. Structure, chemical synthesis, and biosynthesis of Prodiginine natural products. *Chem. Rev.* **2016**, *116*, 7818–7853. [[CrossRef](#)] [[PubMed](#)]
14. Wood, T.E.; Thompson, A. Advances in the chemistry of dipyrroles and their complexes. *Chem. Rev.* **2007**, *107*, 1831–1861. [[CrossRef](#)] [[PubMed](#)]
15. Ding, Y.; Zhu, W.H.; Xie, Y. Development of ion chemosensors based on porphyrin analogues. *Chem. Rev. ASAP* **2016**. [[CrossRef](#)] [[PubMed](#)]
16. Huang, K.H.; Veal, J.M.; Fadden, R.P.; Rice, J.W.; Eaves, J.; Strachan, J.; Barabasz, A.F.; Foley, B.E.; Barta, T.E.; Ma, W.; et al. Discovery of novel 2-aminobenzamide inhibitors of heat shock protein 90 as potent, selective and orally active antitumor agents. *J. Med. Chem.* **2009**, *52*, 4288–4305. [[CrossRef](#)] [[PubMed](#)]
17. Zhao, R.; Sun, Z.; Mo, M.; Peng, F.; Shao, Z. Catalytic asymmetric assembly of C3-monosubstituted chiral carbazolones and concise formal synthesis of (–)-Aspidofractinine: Application of enantioselective Pd-catalyzed decarboxylative protonation of carbazolones. *Org. Lett.* **2014**, *16*, 4178–4181. [[CrossRef](#)] [[PubMed](#)]

18. Shanab, K.; Schirmera, E.; Wulza, E.; Weissenbachera, B.; Lassniga, S.; Slanza, R.; Fösleitner, G.; Holzera, W.; Spreitzer, H.; Peter Schmidt, B.A.; et al. Synthesis and antiproliferative activity of new cytotoxic azanaphthoquinone pyrrolo-annelated derivatives: Part II. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3117–3121. [[CrossRef](#)] [[PubMed](#)]
19. Barton, D.H.R.; Zard, S.Z. A new synthesis of pyrroles from nitroalkenes. *J. Chem. Soc. Chem. Commun.* **1985**, *16*, 1098–1100. [[CrossRef](#)]
20. Amarnath, V.; Anthony, D.C.; Amarnath, K.; Valentine, W.M.; Wetterau, L.A.; Graham, D.G. Intermediates in the Paal-Knorr synthesis of pyrroles. *J. Org. Chem.* **1991**, *56*, 6924–6931. [[CrossRef](#)]
21. Minetto, G.; Raveglia, L.F.; Taddei, M. Microwave-assisted Paal—Knorr reaction. A rapid approach to substituted pyrroles and furans. *Org. Lett.* **2004**, *6*, 389–392. [[CrossRef](#)] [[PubMed](#)]
22. Moss, T.A.; Nowak, T. Synthesis of 2,3-dicarbonylated pyrroles and furans via the three-component Hantzsch reaction. *Tetrahedron Lett.* **2012**, *53*, 3056–3060. [[CrossRef](#)]
23. Herath, A.; Cosford, N.D.P. One-step continuous flow synthesis of highly substituted pyrrole-3-carboxylic acid derivatives via in situ hydrolysis of tert-butyl esters. *Org. Lett.* **2010**, *12*, 5182–5185. [[CrossRef](#)] [[PubMed](#)]
24. Tang, X.; Huang, L.; Qi, C.; Wu, W.; Jiang, H. An efficient synthesis of polysubstituted pyrroles via copper-catalyzed coupling of oxime acetates with dialkyl acetylenedicarboxylates under aerobic conditions. *Chem. Commun.* **2013**, *49*, 9597–9599. [[CrossRef](#)] [[PubMed](#)]
25. Estévez, V.; Villacampa, M.; Menéndez, J.C. Recent advances in the synthesis of pyrroles by multicomponent reactions. *Chem. Soc. Rev.* **2014**, *43*, 4633–4657. [[CrossRef](#)] [[PubMed](#)]
26. Estévez, V.; Villacampa, M.; Menéndez, J.C. Multicomponent reactions for the synthesis of pyrroles. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421. [[CrossRef](#)] [[PubMed](#)]
27. Wu, X.F.; Neuman, H.; Beller, M. Synthesis of heterocycles via palladium-catalyzed carbonylations. *Chem. Rev.* **2013**, *113*, 1–35. [[CrossRef](#)] [[PubMed](#)]
28. Wu, X.F.; Neumann, H. Zinc-catalyzed organic synthesis: C–C, C–N, C–O bond formation reactions. *Adv. Synth. Catal.* **2012**, *354*, 3141–3160. [[CrossRef](#)]
29. Thirumalairajan, S.; Pearce, B.M.; Thompson, A. Chiral molecules containing the pyrrole framework. *Chem. Commun.* **2010**, *46*, 1797–1812. [[CrossRef](#)] [[PubMed](#)]
30. Chen, F.; Shen, T.; Cui, Y.; Jiao, N. 2,4- vs. 3,4-disubstituted pyrrole synthesis switched by copper and nickel catalysts. *Org. Lett.* **2012**, *14*, 4926–4929. [[CrossRef](#)] [[PubMed](#)]
31. Ramanathan, B.; Keith, A.J.; Armstrong, D.; Odom, A.L. Pyrrole syntheses based on titanium-catalyzed hydroamination of diynes. *Org. Lett.* **2004**, *6*, 2957–2960. [[CrossRef](#)] [[PubMed](#)]
32. Wang, L.; Ackermann, L. Versatile pyrrole synthesis through ruthenium(II)-catalyzed alkene C–H bond functionalization on enamines. *Org. Lett.* **2013**, *15*, 176–179. [[CrossRef](#)] [[PubMed](#)]
33. Qi, X.; Xu, X.; Park, C.M. Facile synthesis of 2-alkyl/aryloxy-2H-azirines and their application in the synthesis of pyrroles. *Chem. Commun.* **2012**, *48*, 3996–3998. [[CrossRef](#)] [[PubMed](#)]
34. Zhang, L.; Xu, X.; Shao, Q.; Pan, L.; Liu, Q. Tandem Michael addition/isocyanide insertion into the C–C bond: a novel access to 2-acylpyrroles and medium-ring fused pyrroles. *Org. Biomol. Chem.* **2013**, *11*, 7393–7399. [[CrossRef](#)] [[PubMed](#)]
35. Lonzi, G.; López, L.A. Regioselective synthesis of functionalized pyrroles via gold(I)-catalyzed [3+2] cycloaddition of stabilized vinyl diazo derivatives and nitriles. *Adv. Synth. Catal.* **2013**, *355*, 1948–1954. [[CrossRef](#)]
36. Louillat, M.L.; Patureau, F.W. Oxidative C–H amination reactions. *Chem. Soc. Rev.* **2014**, *43*, 901–910. [[CrossRef](#)] [[PubMed](#)]
37. Cho, S.W.; Kim, J.Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C–H bond activation strategy for C–C and C–N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. [[CrossRef](#)] [[PubMed](#)]
38. Tsang, W.C.P.; Zheng, N.; Buchwald, S.L. Combined C–H functionalization/C–N bond formation route to carbazoles. *J. Am. Chem. Soc.* **2005**, *127*, 14560–14561. [[CrossRef](#)] [[PubMed](#)]
39. Yang, G.; Shen, C.; Zhang, W. An asymmetric aerobic Aza-Wacker-type cyclization: Synthesis of isoindolinones bearing tetrasubstituted carbon stereocenters. *Angew. Chem. Int. Ed.* **2012**, *51*, 9141–9145. [[CrossRef](#)] [[PubMed](#)]
40. Nadres, E.T.; Daugulis, O. Heterocycle synthesis via direct C–H/N–H coupling. *J. Am. Chem. Soc.* **2012**, *134*, 7–10. [[CrossRef](#)] [[PubMed](#)]

41. Obora, Y.; Ishii, Y. Palladium-catalyzed intermolecular oxidative amination of alkenes with amines, using molecular oxygen as terminal oxidant. *Catalysts* **2013**, *3*, 794–810. [[CrossRef](#)]
42. Louillat, M.L.; Patureau, F.W. Toward polynuclear Ru-Cu catalytic dehydrogenative C–N bond formation on the reactivity of carbazoles. *Org. Lett.* **2013**, *15*, 164–167. [[CrossRef](#)] [[PubMed](#)]
43. Yu, D.G.; Suri, M.; Glorius, F. Rh^{III}/Cu^{II}-cocatalyzed synthesis of 1H-Indazoles through C–H amidation and N–N Bond formation. *J. Am. Chem. Soc.* **2013**, *135*, 8802–8805. [[CrossRef](#)] [[PubMed](#)]
44. Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. Ir(III)-catalyzed mild C–H amidation of arenes and alkenes: An efficient usage of acyl azides as the nitrogen source. *J. Am. Chem. Soc.* **2013**, *135*, 12861–12868. [[CrossRef](#)] [[PubMed](#)]
45. Wendlandt, A.E.; Suess, A.M.; Stahl, S.S. Copper-catalyzed aerobic oxidative C–H functionalizations: Trends and mechanistic insights. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062–11087. [[CrossRef](#)] [[PubMed](#)]
46. Weinstein, A.B.; Schuman, D.P.; Tan, Z.X.; Stahl, S.S. Synthesis of vicinal aminoalcohols by stereoselective aza-Wacker cyclizations: Access to (–)-Acosamine by redox relay. *Angew. Chem. Int. Ed.* **2013**, *52*, 11867–11870. [[CrossRef](#)] [[PubMed](#)]
47. Redford, J.E.; McDonald, R.I.; Rigsby, M.L.; Wiensch, J.D.; Stahl, S.S. Stereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines via Wacker-type aerobic oxidative cyclization of alkenes with tert-butanefulfonamide nucleophiles. *Org. Lett.* **2012**, *14*, 1242–1245. [[CrossRef](#)] [[PubMed](#)]
48. Zhang, Z.; Zhang, J.; Tan, J.; Wang, Z. A facile access to pyrroles from amino acids via an Aza-Wacker cyclization. *J. Org. Chem.* **2008**, *73*, 5180–5182. [[CrossRef](#)] [[PubMed](#)]
49. Yip, K.T.; Yang, M.; Law, K.L.; Zhu, N.Y.; Yang, D. Pd(II)-catalyzed enantioselective oxidative tandem cyclization reactions. Synthesis of indolines through C–N and C–C bond formation. *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131. [[CrossRef](#)] [[PubMed](#)]
50. Yang, G.; Zhang, W. Regioselective Pd-catalyzed aerobic Aza-Wacker cyclization for preparation of isoindolinones and isoquinolin-1(2H)-ones. *Org. Lett.* **2012**, *14*, 268–271. [[CrossRef](#)] [[PubMed](#)]
51. Ramirez, T.A.; Zhao, B.; Shi, Y. Recent advances in transition metal-catalyzed sp³ C–H amination adjacent to double bonds and carbonyl groups. *Chem. Soc. Rev.* **2012**, *41*, 931–942. [[CrossRef](#)] [[PubMed](#)]
52. Butt, A.N.; Zhang, W. Synthesis of heterocycles via palladium catalyzed Wacker-type oxidative cyclization reactions of hydroxy- and amino-alkenes. In *Topics in Heterocyclic Chemistry*; Wolfe, J.P., Ed.; Springer: Berlin/Heidelberg, Germany, 2013.
53. Obora, Y.; Shimizu, Y.; Ishii, Y. Intermolecular oxidative amination of olefins with amines catalyzed by the Pd(II)/NPMoV/O₂ system. *Org. Lett.* **2009**, *11*, 5058–5061. [[CrossRef](#)] [[PubMed](#)]
54. Mizuta, Y.; Yasuda, K.; Obora, Y. Palladium-catalyzed Z-selective oxidative amination of *ortho*-substituted primary anilines with olefins under an open air atmosphere. *J. Org. Chem.* **2013**, *78*, 6332–6337. [[CrossRef](#)] [[PubMed](#)]
55. Wu, X.F.; Neumann, H.; Beller, M. Palladium-catalyzed oxidative carbonylation reactions. *ChemSusChem* **2013**, *6*, 229–241. [[CrossRef](#)] [[PubMed](#)]
56. Takenaka, K.; Mohanta, S.C.; Patil, M.L.; Rao, C.V.L.; Takizawa, S.; Suzuki, T.; Sasai, H. Enantioselective Wacker-type cyclization of 2-alkenyl-1,3-diketones promoted by Pd-SPRIX catalyst. *Org. Lett.* **2010**, *12*, 3480–3483. [[CrossRef](#)] [[PubMed](#)]
57. Takenaka, K.; Akita, M.; Tanigaki, Y.; Takizawa, S.; Sasai, H. Enantioselective cyclization of 4-alkenoic acids via an oxidative allylic C–H esterification. *Org. Lett.* **2011**, *13*, 3506–3509. [[CrossRef](#)] [[PubMed](#)]
58. Yang, W.; Huang, L.; Liu, H.; Wang, W.; Li, H. Efficient synthesis of highly substituted pyrroles through a Pd(OCOCF₃)₂-catalyzed cascade reaction of 2-alkenyl-1,3-dicarbonyl compounds with primary amines. *Chem. Commun.* **2013**, *49*, 4667–4669. [[CrossRef](#)] [[PubMed](#)]
59. Yu, Y.; Liu, Y.; Liu, A.; Xie, H.; Li, H.; Wang, W. Ligand-free Cu-catalyzed [3+2] cyclization for the synthesis of pyrrolo[1,2-*a*]quinolines with ambient air as a terminal oxidant. *Org. Biomol. Chem.* **2016**, *14*, 7455–7458. [[CrossRef](#)] [[PubMed](#)]
60. Xu, L.; Li, H.; Liao, Z.; Lou, K.; Xie, H.; Li, H.; Wang, W. Divergent synthesis of imidazoles and quinazolines via Pd(OAc)₂-catalyzed annulation of *N*-allylamidines. *Org. Lett.* **2015**, *17*, 3434–3537. [[CrossRef](#)] [[PubMed](#)]
61. Wang, H.; Yang, W.; Liu, H.; Wang, W.; Li, H. FeCl₃ promoted highly regioselective [3+2] cycloaddition of dimethyl 2-vinyl and aryl cyclopropane-1,1-dicarboxylates with aryl isothiocyanates. *Org. Biomol. Chem.* **2012**, *10*, 5032–5035. [[CrossRef](#)] [[PubMed](#)]

62. Chen, J.; Li, J.; Wang, J.; Li, H.; Wang, W.; Guo, Y. Phosphine-catalyzed Aza-MBH reactions of vinylpyridines: Efficient and rapid access to 2,3,5-triarylsubstituted 3-pyrrolines. *Org. Lett.* **2015**, *17*, 2214–2217. [[CrossRef](#)] [[PubMed](#)]
63. Wang, S.; Yu, Y.; Chen, X.; Zhu, H.; Du, P.; Liu, G.; Lou, L.; Li, H.; Wang, W. FeCl₃-catalyzed selective acylation of amines with 1,3-diketones via C–C bond cleavage. *Tetrahedron Lett.* **2015**, *56*, 3093–3096. [[CrossRef](#)]
64. Zhang, X.S.; Song, X.X.; Li, H.; Zhang, S.L.; Chen, X.B.; Yu, X.H.; Wang, W. An organocatalytic cascade approach toward polysubstituted quinolines and chiral 1,4-dihydroquinolines—unanticipated effect of N-protecting groups. *Angew. Chem. Int. Ed.* **2012**, *51*, 7282–7286. [[CrossRef](#)] [[PubMed](#)]
65. Zu, L.; Xie, H.; Li, H.; Wang, J.; Yu, X.H.; Wang, W. Chiral amine-catalyzed enantioselective cascade Aza–Ene-type cyclization reactions. *Chem. Eur. J.* **2008**, *14*, 6333–6335. [[CrossRef](#)] [[PubMed](#)]
66. Barraja, P.; Diana, P.; Lauria, A.; Montalbano, A.; Almerico, A.M.; Dattolo, G.; Cirrincione, G.; Violab, G.; Dall’Acqua, F. Pyrrolo[2,3-*h*]quinolinones: Synthesis and photochemotherapeutic activity. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2809–2811. [[CrossRef](#)]
67. Chacón-García, L.; Martínez, R. Synthesis and in vitro cytotoxic activity of pyrrolo[2,3-*e*]indole derivatives and a dihydro benzoindole analogue. *Eur. J. Med. Chem.* **2002**, *37*, 261–266. [[CrossRef](#)]
68. Martínez, R.; Ávila, J.G.; Ramírez, M.T.; Pérez, A.; Martínez, Á. Tetrahydropyrrolo[3,2-*c*]azepin-4-ones as a new class of cytotoxic compounds. *Bioorg. Med. Chem.* **2006**, *14*, 4007–4016. [[CrossRef](#)] [[PubMed](#)]



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