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A Novel Approach to *N*-Tf 2-Aryl-2,3-Dihydroquinolin-4(1*H*)-ones via a Ligand-Free Pd(II)-Catalyzed Oxidative Aza-Michael Cyclization

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Abstract: 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones have recently been identified as important structures with potent biological activities such as antitumor and antidiabetic effect. Herein, a total of 25 novel *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones were expediently synthesized via the oxidative aza-Michael cyclization of *N*-Tf-2′-aminodihydrochalcones by ligand-free palladium(II) catalysis. This study presents a new synthetic approach to yield *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones, which can be easily transformed into pharmacologically interesting aza-flavanones and other *N*-heterocycles, such as quinolines and tetrahydroquinolines, in yields up to 84%. This methodology has various advantages, which includes short reaction times under mild conditions and suitable functional group tolerance. Furthermore, a plausible mechanism was proposed and demonstrated by kinetic analysis.

Flavonoids are a common class of natural products and their synthetic analogs, frequently serving as pharmaceutical agents with numerous biological activities.[1] Recently, 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones which are also known as aza-flavanones in which the *N* is substituted for an *O* in the flavanone structure, have been considered novel privileged structures found in a variety of antitumor[2] and antidiabetic[3] agents, cross-species microRNA inhibitors,[4] and PARP inhibitors (Figure 1).[5] Furthermore, 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones can be transformed into various nitrogen-bearing heterocycles, such as tetrahydroquinoline, quinoline and quinolone, which are key motifs in active pharmaceutical ingredients.[6] Thus, several synthetic transformations have been developed over a number of years for the prevalence of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones. Intermolecular condensation reactions, such as Mannich reaction or aldol condensation, between *o*-aminoacetophenones and aryl aldehydes have been well known to promote the formation of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones in a one-pot fashion.[7] The majority of these cascade reactions relies upon the use of organocatalysts or Lewis acid catalysts with relatively long reaction times. Alternatively, the intramolecular cyclization of 2′-aminochalcones has also been developed in the presence of Lewis acid catalysts,[8] acids,[9] bases,[10] or ionic liquids.[11] These Michael addition type of reactions yield in moderate to good yields but often require harsh reaction conditions. In addition, 2′-

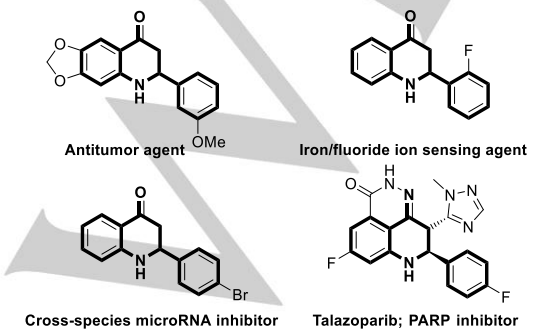
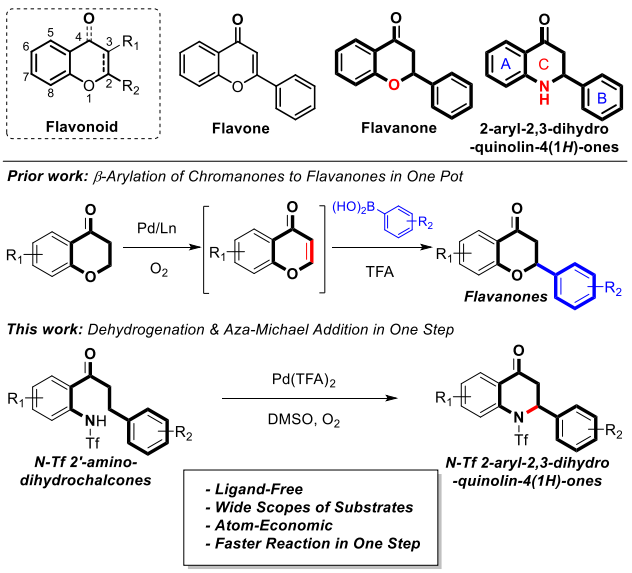
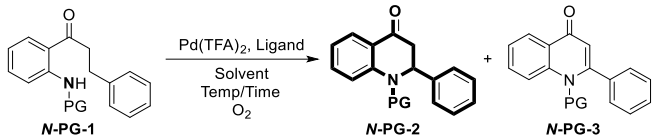


Figure 1. Examples of biologically active 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones.



Scheme 1. Synthetic approach to *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones.

Table 1. Optimization experiments for the selective synthesis of *N*-Tf 2-phenyl-2,3-dihydroquinolin-4(1*H*)-ones **2**.[a]



Entry	PG	Ligand	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	
						2	**3**
1	-	5-NO_2-phen	DMSO	100	48	n.r	n.r
2	Ms	5-NO_2-phen	DMSO	100	48	48	9
3	Ms	bpy	DMSO	100	48	26	7
4	Ms	pyridine	DMSO	100	48	43	19
5	Ms	DMAP	DMSO	100	48	50	28
6	Tf	DMAP	DMSO	100	2	62	12
7	Tf	DMAP	DMSO	80	2	65	6
8	Tf	-	DMSO	80	2	83	7
9	Tf	-	DMF	80	2	20	6
10	Tf	-	1,4-dioxane	80	2	n.r	n.r
11	Tf	-	*n*-BuOH	80	2	n.r	n.r
12	Tf	-	toluene	80	2	n.r	n.r
13[c]	Tf	-	DMSO	80	2	65	3
14[d]	Tf	-	DMSO	80	2	20	1
15[e]	Tf	-	DMSO	80	2	70	13
16	Tf	-	DMSO	80	24	61	15
17[f]	Tf	-	DMSO	80	2	13	0
18[g]	Tf	-	DMSO	80	2	11	2
19[h]	Tf	-	DMSO	80	2	28	4
20[i]	Tf	-	DMSO	80	2	70	4

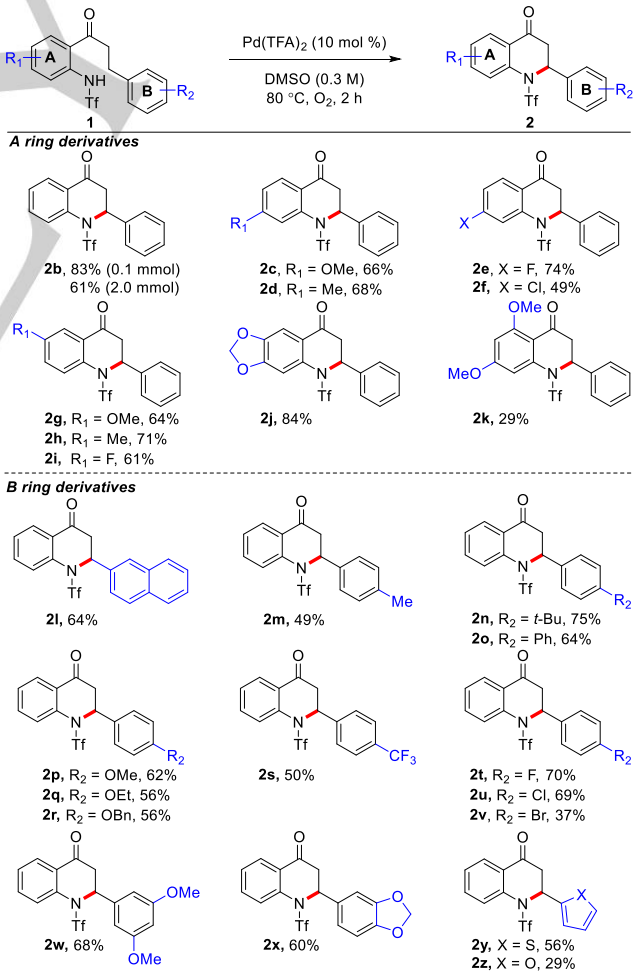
[a] Reaction conditions: **1** (0.1 mmol), $Pd(TFA)_2$ (10 mol %), ligand (20 mol %), and solvent (0.3 mL) under O_2 for 2–48 h. [b] Isolated yield. [c] $Pd(TFA)_2$ (5 mol %). [d] $Pd(OPiv)_2$ was used instead of $Pd(TFA)_2$. [e] $Pd(OAc)_2$ was used instead of $Pd(TFA)_2$. [f] $Cu(OAc)_2$ (0.1 mmol, 1 equiv) was used instead of O_2 under argon. [g] $Cu(OAc)_2$ (0.2 mmol, 2 equiv) was used instead of O_2 under argon. [h] MnO_2 (0.1 mmol, 1 equiv) was used instead of O_2. [i] AgOAc (0.1 mmol, 1 equiv) was used instead of O_2.

aminochalcones, traditional intermediates or substrates of these reactions are sometimes unmanageable due to their reactive *α,β*-unsaturated carbonyls. Therefore, there has been a growing need to develop an efficient approach to synthesize 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones from chemically compatible substrates equipped with structural diversity under mild reaction conditions.

Recently, we developed the palladium(II)-catalyzed one-pot *β*-arylation of chromanones, a kind of simple and tolerable ketones, with arylboronic acids via a dehydrogenation/conjugate sequence for the synthesis of flavanones (Scheme 1).[12] Based on our previous study, we herein report a novel approach to synthesize *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones from manageable *N*-Tf-2′-aminodihydrochalcones via Pd(II)-catalyzed dehydrogenation followed by intramolecular aza-Michael addition. In particular, the attractive features of this method include the in situ formation of 2′-aminochalcones for 1,4-addition using $Pd(TFA)_2$ without ligands under mild conditions.

Initial experiments involving the reaction of *N*-protected-1-(2-aminophenyl)-3-phenylpropanone (*N*-PG-**1**) were inspired by the established conditions for palladium(II)-catalyzed *β*-arylation of chromanones in our previous report. The experiment with 1-(2-aminophenyl)-3-phenylpropanone **1** failed ligand in DMSO under an O_2 atmosphere because of the potential to form 2-phenyl-2,3-dihydroquinolin-4(1*H*)-ones **2** in the presence of $Pd(TFA)_2$ as the catalyst and 5-NO_2-phen as the coordination between free amine and the Pd(II) catalyst to suppress aminopalladation (Table 1, entry 1).[13] Thus, Ms group was introduced as a protecting group to prevent the coordination effect of the free amine in **1**. Several reactions involving *N*-Ms-**1** as a model compound were conducted with the use of various ligands, such as 5-NO_2-phen, bpy, pyridine, and DMAP (entries 2–5).

Table 2. Scope for the synthesis of *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones **2**.[a],[b]



[a] Reaction conditions: **1** (0.1 mmol), $Pd(TFA)_2$ (10 mol %), and DMSO (0.3 mL) at 80 °C under O_2 for 2 h. [b] Isolated yield.

Consequently, a mixture of *N*-Ms 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **2a** and *N*-Ms 2-phenylquinolin-4(1*H*)-one **3a** was obtained. Upon use of *N*-Tf-**1**, it was observed that the second dehydrogenation pathway that occurred via *β*-hydride elimination was suppressed, which might have resulted from the relatively unstable transition state induced by increased electron withdrawing effect of Tf compared to Ms, delivering the desired product, *N*-Tf-**2** (**2b**) and undesired product, *N*-Tf-**3** (**3b**), in 62% and 12% isolated yields, respectively (entry 6). Remarkably, the ligand-free system enables the reaction to afford the desired 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **2b** in the highest yield of 83% (entries 7 and 8) with a lower reaction temperature (80 °C), and a shorter reaction time (2 h) than those reactions under other conditions. Further variation in the solvent (entries 9–12), catalyst loading amount (entry 13), type of catalysts (entries 14 and 15), reaction time (entry 16), and oxidants (entries 17–20) did not provide additional improvement.

Under the optimal conditions, the reactions of a variety of **A** ring derivatives of *N*-Tf-2′-aminodihydrochalcones **1** were performed to investigate the functional group compatibility of the reaction (Table 2, top section). A series of substrates with electroneutral (**1b**), electron donating (**1c**–**1d** and **1g**–**1h**), and electron withdrawing (**1e**–**1f** and **1i**) groups on the **A** ring were successfully transformed into the desired products **2b**–**2i**, respectively, in moderate to good yields. The scaled-up cyclization reaction was also successfully performed on a 2.0 mmol scale and **2b** was obtained in a yield of 61%. Furthermore, it was found that heteroaryl **A** ring such as 1,3-benzodioxole (**1j**) successfully engaged in C–N bond formation in 84% isolated yield. However, the reaction was relatively inefficient for the preparation of **2k**, which included a dimethoxy group. Subsequently, to further broaden the scope of this method, the reactions of the *N*-Tf-2′-aminodihydrochalcones **1** with a variety of aryl or heteroaryl **B** rings were also performed under the optimized reaction conditions (Table 2, bottom section). Various aryl **B** rings containing either electron-donating (alkyl, aryl, OMe, OEt, OBn, and 1,3-benzodioxole) or electron-withdrawing (CF_3 and halogens) groups were explored, and the corresponding products **2l**–**2x** were obtained in 37 to 75% yield. Relatively, C–N bond formation of *N*-Tf-1-(2-aminophenyl)-3-(4-bromophenyl)propanone **1v** was less productive because the 4-bromophenyl group would presumably participate in oxidative addition in the presence of the Pd(0) catalyst species. Moreover, the reactions with a heteroaryl **B** ring (thiophene and furan) delivered the desired adducts **2y**–**2z** in 56% and 29% yield, respectively.

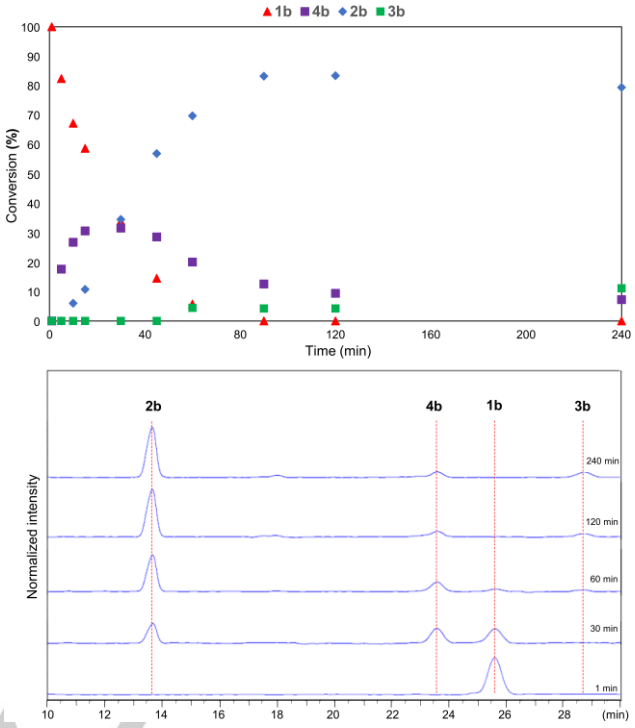
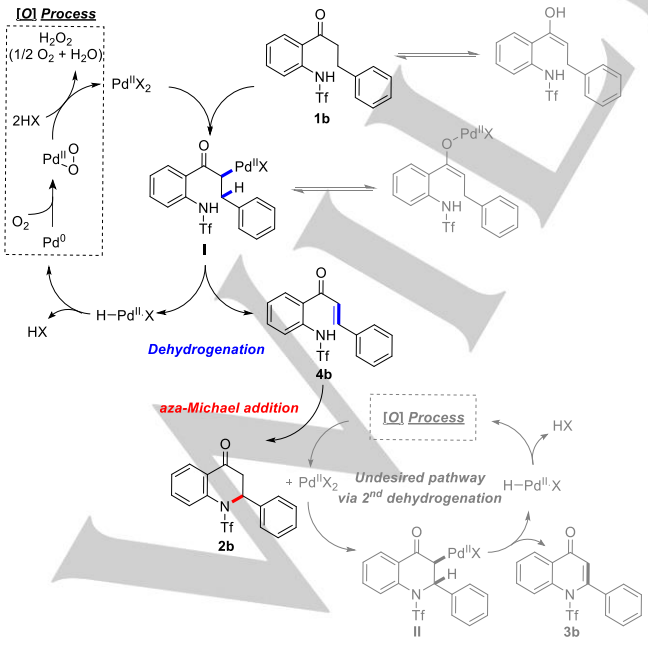


Figure 2. Mechanism study by kinetic analysis

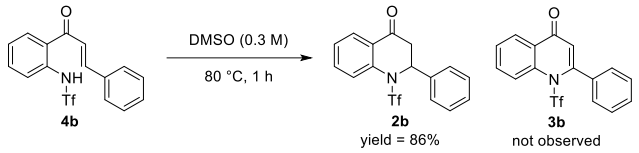
A plausible mechanism involving the dehydrogenation/aza-Michael cyclization sequence for the synthesis of *N*-Tf 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **2b** is illustrated in Scheme 2. Based on our prior mechanistic studies,[12] it is plausible that *N*-Tf-2′-aminodihydrochalcone **1b** might react with Pd(II)X_2 to form Pd(II) complex **I** via C–H palladation.[14] *β*-Hydride elimination of **I** delivers a key intermediate, *N*-Tf-2′-aminochalcone **4b**, accompanied by HPd(II)X which undergoes reductive elimination to afford the Pd(0) species.[15] In the Pd(II)-catalyzed oxidation condition, benzylic carbon could be easily oxidized and transformed into a carbocation which is enabled to make the cyclization (for **2b**) or E1 type elimination (for **4b**).[16] To elucidate whether the reaction occurs via *β*-hydride elimination or benzylic oxidation, we performed a reaction of the substrate without terminal aryl substituent, **1aa**, in the optimized condition. It provided the anticipated product **2aa** with good yield, suggesting that the reaction might be progressed via *β*-hydride elimination step (Supporting Information, p. 57). Finally, the [O] process generates Pd(II)X_2 in the presence of O_2 as an oxidant to regenerate the Pd(II)-catalyzed dehydrogenation cycle.[17] Subsequently, key intermediate **4b** converts to the desired product **2b** through aza-Michael cyclization.[18] In the case of the formation of *N*-Tf 2-phenylquinolin-4(1*H*)-one **3b**, **2b** would



Scheme 2. A plausible mechanism of the reaction.

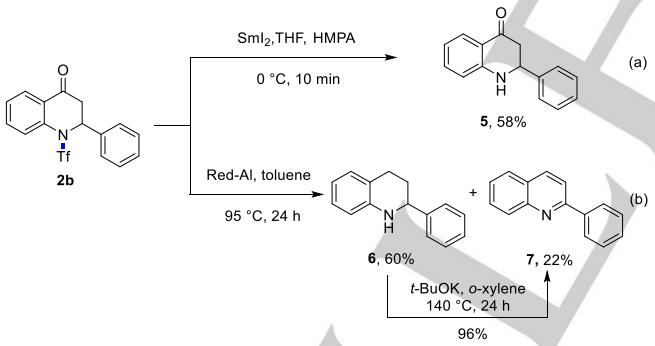
additionally undergo C–H palladation followed by *β*-hydride elimination in an undesired pathway.[19] Thus, in order to selectively synthesize **2b** in good yield, it is likely that second dehydrogenation should be suppressed.

To corroborate the proposed mechanism, kinetic analysis of the reaction was performed by a time-dependent conversion experiment of **1b** under the optimized reaction conditions (Figure 2). As anticipated, gradual formation of key intermediate **4b** and subsequent conversion into the desired **2b** was observed by HPLC analysis over time. After 1 h, **1b** was completely consumed, and the undesired **3b** began to be generated. Thus, based on these experiments, short reaction time is required to prevent the formation of **3b**.



Scheme 3. Control experiment for the intramolecular aza-Michael cyclization.

In order to confirm whether the Pd(II) catalyst is significantly involved in the 1,4-addition, further intramolecular 1,4-addition experiments were performed in the absence of $Pd(TFA)_2$ (Scheme 3). Consequently, **2b** was obtained in 86% isolated yield from **4b** with 1 h, while undesired product **3b** was not observed. This control experiment indicated that the 1,4-addition could occur through aza-Michael addition without $Pd(TFA)_2$ and that catalysis might be more crucial for the dehydrogenation process than for the aza-Michael cyclization.



Scheme 4. *N*-Tf deprotection, and synthesis of quinoline derivatives.

Finally, deprotection of the triflate protecting group was conducted to synthesize aza-flavanone **5** in 58% yield under mild SmI_2 reduction condition (Scheme 4, a).[20] Furthermore, we tried to synthesize quinoline derivatives from *N*-Tf 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one **2b** (Scheme 4, b). Tetrahydroquinoline **6** was successfully produced by Red-Al reduction along with minor product quinoline **7**, which could be easily converted from **6** by dehydrogenation in excellent yield.[21]

In summary, we reported a novel approach to synthesize *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-one via Pd(II)-catalyzed dehydrogenation followed by aza-Michael cyclization. This protocol enables the rapid synthesis of *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-one derivatives, which could potentially be converted into pharmacologically interesting aza-flavanones and other *N*-heterocycles such as quinolines, in up to 84% yield under mild conditions. In addition, this reaction has several advantageous features, including being ligand-free and atom-economic, and offering good compatibility with a wide scope of substrates. Mechanistic studies were successfully conducted by HPLC-based kinetic analysis. Further studies will focus on the biological studies using the compounds synthesized by our methodology and the development of another novel methodology for the synthesis of flavonoids and related compounds.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 2-aryl-2,3-dihydroquinolin-4(1*H*)-one • dehydrogenation • Michael addition • palladium • quinoline

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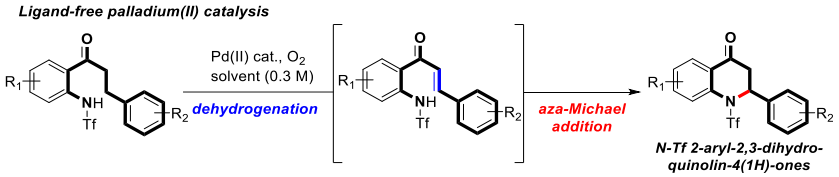

The one-pot ligand-free palladium-catalyzed *α,β*-dehydrogenation of ketone and sequential aza-Micahel addition was developed, which provides *N*-Tf 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones in moderate to good yields. This catalytic reaction provides simple and mild reaction conditions, a wide scope of substrates to biologically interesting *N*-heterocycles.

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