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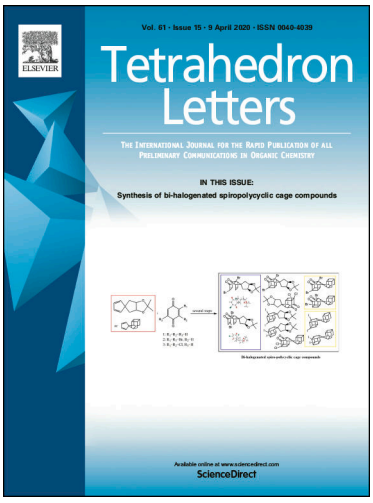

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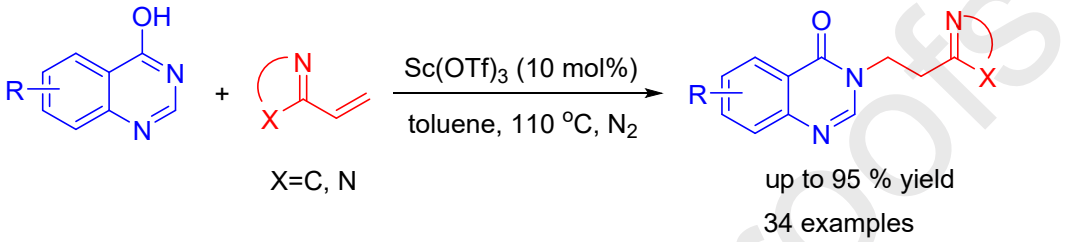

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Scandium-Catalyzed Michael Addition of Quinazolinones and Vinylazaarenes

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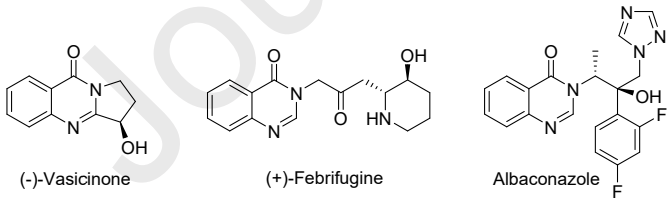
ABSTRACT

We described a novel scandium-catalyzed selective Michael addition of quinazolinones and vinylazaarenes. The protocol proceeds smoothly to give diverse quinazolinone derivatives in moderate to excellent yields. The high practicality of this protocol was proved by excellent chemo selectivity and broad substrate and functional group compatibility.

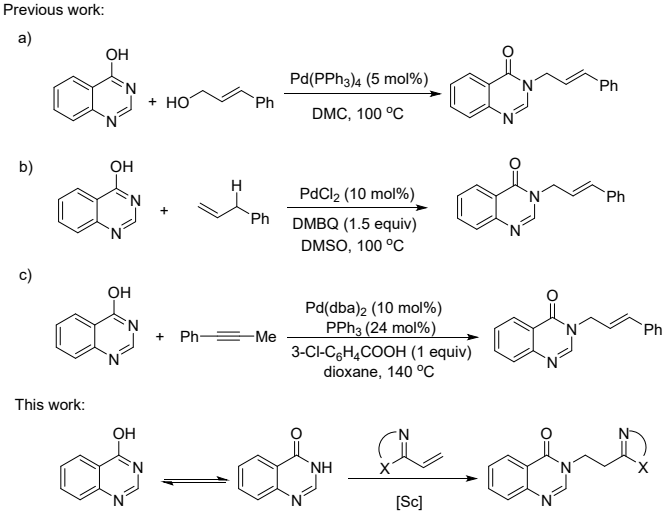
The N-substituted quinazolinones and related tautomerizable heterocycles present frequently in natural products, drug candidates and bioactive molecules.[1] For example, Tryptanthrin is a plant alkaloid displaying anti-inflammatory and anti-cancer activities. Vasicinone, which was found in Peganum harmala, was shown to have antianaphylactic activity (Figure 1). Besides, quinazolinones are also widely used in material science.[2] Although various strategies have been established, it's still highly important to develop novel and effective protocols to accomplish diverse functionalization of quinazolinones.

Figure 1. Quinazolinones derivatives with biological activities



The pursuit of high chemo selectivity is always critical in the process of functioning tautomerizable heterocycles because these substrates have multiple nucleophilic centers.[3] In some reactions, O-alkylated product can be dominant.[4] Thus, achieving N-selectivity in related reactions is always a challenging task. Consequently, much attention has been paid to improving the selectivity of desired N-alkylation reaction.[5] Mechanism of the reactions was also probed to illustrate the reason for the production of N- or O- alkylated products.[3b] To the best of our knowledge, only a few methods have been developed in the functioning of theses tautomerizable heterocycles with high chemo selectivity. In 2015, Cook and coworkers developed Pd-catalyzed chemo- and regioselective allylation of tautomerizable heterocycles with allyl alcohols (Figure 2a).[6] N-alkylated product was obtained in excellent selectivity with high yields. Moreover, they described oxidative allylic amidation of tautomerizable heterocycles with allylbenzene through the modified White's strategy in 2016 (Figure 2b).[7]

Figure 2. Synthesis of quinazolinones derivatives



Meanwhile, Lu and coworkers discovered that the reaction between tautomerizable heterocycles with simple alkynes could afford same product (Figure 2c).[3c] Besides, Breit described the first rhodium-catalyzed allylic reaction between 4-hydroxyquinazoline with allylic carbonates, achieving high chemo-, and regioselectivities.[8] While diverse methods have been developed for synthesizing tautomerizable heterocycle derivatives, very limited addition reaction examples have been

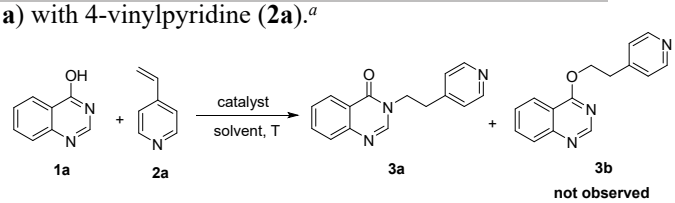
rep e coupling of 2-aryl-4-quinazolinones with olefins through C-H activation/aza-Michael reaction strategy.[9a] Subsequently, Peng found rhodium could also promote these tandem reactions successfully.[9b] Interestingly, Engle reported palladium-catalyzed directed alkene hydroamination between 2-pyridone derivatives and olefins in 2017.[9c] Recently, Hou reported the first aza-Michael addition of 2-hydroxypyridines with α, β-unsaturated 1,4-dicarbonyl compounds with high N-selectivity in 2019.[10]

On the other hand, vinylazaarenes have been successfully employed as novel Michael acceptor by Lam,[11] Wang,[12] Harutyunyan,[13] Terada[14] and Jiang[15] in recent years. A series of nucleophiles such as aldehydes, azoles,[16] amino acid esters,[17] and alkoxyamine[18] have been utilized to react with the novel Michael acceptor.[19] We envisioned whether this methodology could be smoothly transferred to derivatization of tautomerizable heterocycles. Herein, we report the first $Sc(OTf)_3$ catalyzed aza-Michael addition reaction between quinazolinones and vinylazaarenes.

To begin, 4-hydroxyquinazoline (4-quinazolinone) **1a** was selected as a model substrate with two distinct tautomerizable nucleophilic centers (–OH and –NH) to react with 4-vinylpyridine **2a** (Table 1). To our delight, N-alkylated quinazolinone product **3a** was obtained in 54% yield with 10 mol% $Sc(OTf)_3$ catalyst in 3 mL DMSO at 110 °C under an N_2 atmosphere without observing any O-alkylated product (Table1, entry 1). The studies showed that the solvent had a great impact on this reaction. It proved that only 17% yield was observed when the reaction was carried out in THF (entry 4). After screening of solvent, the product **3a** was obtained in 91% yield with toluene as solvent (Table1, entry 9). Next, a series of Lewis acids were tested for the reaction. $Cu(OAc)_2$, $FeCl_3$, $Pd(OAc)_2$, $Pd(PPh)_4$ or $ZnBr_2$ could also promote the reaction with relatively lower yield (entry 10-14). It should be noted that Brønsted acid could also promote the transformation (entry 15). Considering the corrosiveness of HOTf, it was not chosen for catalyzing the reaction. In the absence of catalyst, no reaction was occurred (entry 19). A systematic survey of catalysts revealed that $Sc(OTf)_3$ could promote the reaction most effectively. The yield decreased apparently when the catalyst loading was lowered to 5 mol%. (entry 16) Decreasing reaction temperature results in much lower yield (entry 17). Moreover, the reaction could not proceed at all when the temperature was lowered to 60 °C. (entry 18) Therefore, the optimal reaction condition was confirmed as follow: a solution of **1** (1 equiv), **2** (2 equiv), 10 mol% $Sc(OTf)_3$ in toluene was stirred for 12 h at 110 °C with a N_2 balloon (entry 9).

With the optimal condition in hand, the scope of the reaction between 4-hydroxyquinazoline **1a** and various vinylazaarenes was probed. (Table 2) A wide range of readily accessible vinylazaarenes underwent this reaction with **1a** in excellent chemo selectivity. Generally, 2-vinylpyridines with electron-deficient or electron-rich groups afforded products **3a**-**3f** in moderate to excellent yields (73-89%). In the case of para-substituted substrate **3f**, lower yield was observed compared to **3d** and **3e**. Additionally, the reaction of 4-hydroxyquinazoline with 4-vinylpyridine resulted in 91% yield (**3g**). Next, we examined the reactions for 4-vinylpyridines with different functional groups. It turned out that 4-vinylpyridines with halogen atoms (**3h**-**3k**) such as -Cl, -Br, -F on the ortho-position

(**1a**) with 4-vinylpyridine (**2a**).[a]



entry	catalyst	solvent	T(°C)	yield%[b]
1	$Sc(OTf)_3$	DMSO	110	54
2	$Sc(OTf)_3$	1,4-dioxane	110	43
3	$Sc(OTf)_3$	DMF	110	58
4	$Sc(OTf)_3$	THF	110	17
5	$Sc(OTf)_3$	EtOAc	110	55
6	$Sc(OTf)_3$	DCE	110	42
7	$Sc(OTf)_3$	CH_3CN	110	34
8	$Sc(OTf)_3$	neat	110	56
9	$Sc(OTf)_3$	toluene	110	91
10	$Cu(OAc)_2$	toluene	110	79
11	$FeCl_3$	toluene	110	19
12	$Pd(OAc)_2$	toluene	110	43
13	$Pd(PPh)_4$	toluene	110	71
14	$ZnBr_2$	toluene	110	23
15	HOTf	toluene	110	67
16[c]	$Sc(OTf)_3$	toluene	110	72
17	$Sc(OTf)_3$	toluene	80	56
18	$Sc(OTf)_3$	toluene	60	0
19	-	toluene	110	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), 10 mol% catalyst, in 3 mL solvent at 110 °C for 12 h.

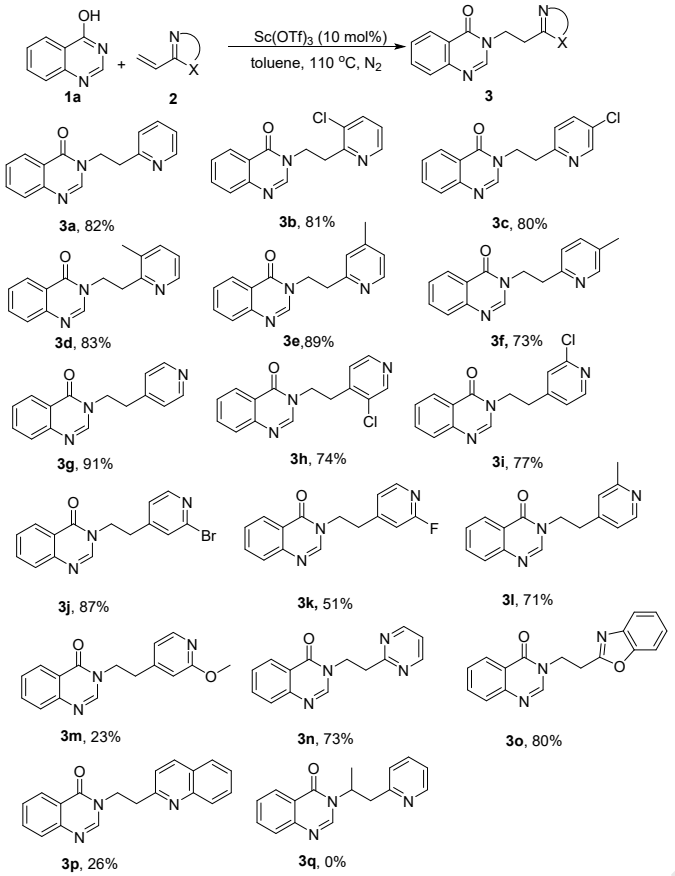
[b] isolated yield.

[c] 5 mol% of $Sc(OTf)_3$ was used as the catalyst.

or meta-position could react with 4-hydroxyquinazoline successfully in 51%-87% yield. It appeared those substrates with electron-donating groups resulted in lower yields (**3l**, **3m**), which may be attributed to the lower reactivity of these compounds. We then explored whether this reaction could be applied for heterocycles other than pyridine. Gratifyingly, heterocycles such as pyrimidine and benzoxazole were well tolerated (**3n**, **3o**) with good yields. But the reaction between **1a** and 2-vinylquinoline afforded product **3p** in 26% yield. Next, it was found that the reaction between **1a** and (*E*)-2-(prop-1-en-1-yl)pyridine couldn't occur, probably due to its lower reactivity (**3q**).

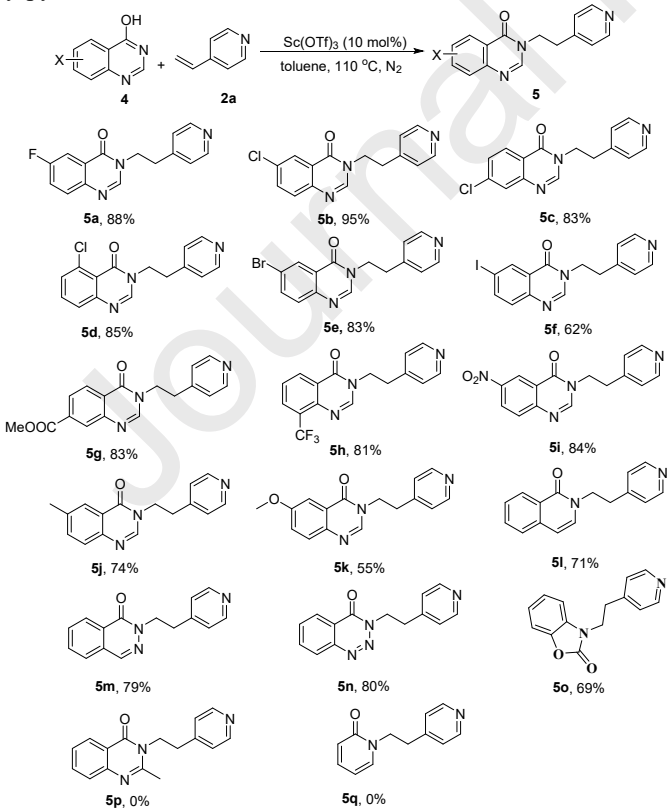
Subsequently, the scope of 4-hydroxyquinazolines was examined for the reaction with 4-vinylpyridine as a standard substrate and the results are shown in Table 3. 4-hydroxyquinazolines with different substituents could react well to produce **5** in moderate to high yields with excellent chemo selectivity. It was found that these 4-hydroxyquinazolines with electron-deficient groups reacted well to afford the adduct product in 62-95% yields (Table 3, **5a**-**5i**). Besides, the position of substituent groups on the phenyl didn't affect the reaction apparently (**5b**-**5d**). 4-hydroxyquinazolines with electron-rich groups on the phenyl afforded 55-74% yield (**5j**, **5k**), indicating

Tab he quinazolinone **1a**[a]



[a] General condition: **1a** (0.5 mmol), **2a** (1.0 mmol), $Sc(OTf)_3$ (0.05 mol), toluene (3 mL), isolated yields are given.

Table 3. Range of quinazolinones in reaction with 4-vinylpyridine **2a**[a]

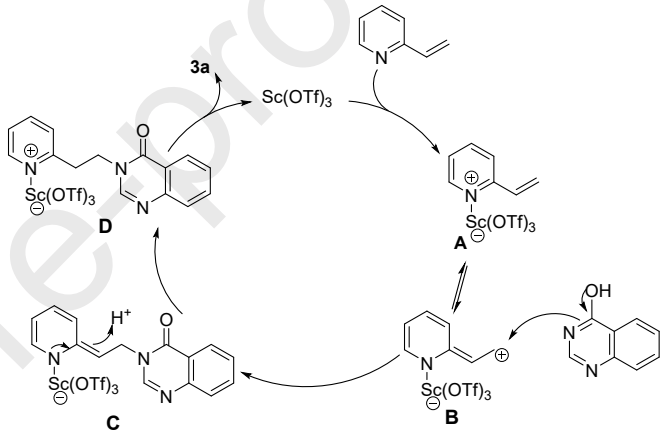


[a] General condition: **4** (0.5 mmol), **2a** (1.0 mmol), $Sc(OTf)_3$ (0.05 mol), toluene (3 mL), isolated yields are given.

substrates. However, 2-substituted quinazolinones couldn't react with **2a** to afford the desired product probably due to the steric effects (**5p**). Furthermore, other biologically relevant tautomerizable heteroarenes were tested to prove the applicability of this method. To our delight, heterocycles such as isoquinolinone (**5l**), phthalazinone (**5m**), benzo[d][1,2,3]triazin-4(3H)-one (**5n**) and 2-benzoxazolinone (**5o**) all reacted smoothly with medium to good yields under the optimal condition. Unfortunately, pyridin-2-ol couldn't react with **2a** under the standard condition (**5q**).

The proposed mechanism of this addition reaction was shown in Figure 3. The nitrogen of 2-vinylpyridine was activated by $Sc(OTf)_3$ to produce polarized intermediate structure **A**, which was converted to intermediate **B** with positive charge at the terminal carbon. Then the intermediate **C** was obtained by the conjugate addition of 4-hydroxypyridine. Subsequently, intermediate **D** was produced through protonation. Finally, $Sc(OTf)_3$ was recycled to afford the final product **3a**.

Figure 3. Proposed mechanism for the reaction.



In conclusion, we have developed an efficient protocol for the synthesis of N-substituted quinazolinones. This new strategy may be a better choice for the synthesis of quinazolinone derivatives owing to excellent N-selectivity and the relatively broad scopes of both the tautomerizable heterocycles and vinylazaarenes substrates. Further investigation of this methodology in the synthesis of bioactive molecules are undergoing in our laboratories.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file.

Hig

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