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Direct Alkenylation of 2-Methylquinolines with Aldehydes through Synergistic Catalysis of 1,3-Dimethylbarbituric Acid and HOAc

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Abstract: An efficient and practical direct alkenylation of 2-methylquinolines with aldehydes has been achieved through a novel synergistic organocatalysis. The HOAc-activated 2-methylquiolines undergo a Michael addition to 1,3-dimethylbarbituric acid-activated aldehydes, followed by a retro-Michael addition to release 1,3-dimethylbarbituric acid and the target products. The transformation produced various 2-alkenylquinolines with good to excellent yields and featured mild reaction conditions, atom- and step-economy, good functional group tolerance, and operational simplicity.

Keywords: synergistic catalysis; organocatalysis; alkenylation; 2-methylquinolines;

Organocatalysis has many advantages, including easy accessibility, insensitivity towards to oxygen and moisture, economy and non-toxicity.[1] Moreover, transformations with organocatalysis usually proceed in mild reaction conditions with broad substrate scope and excellent functional group tolerance. Synergistic catalysis combinating two distinct catalytic systems in one reaction has received intensive attention in recent years.[2] The typically synergistic system was constituted by the metal catalysis and organocatalysis or bimetallic system.[3] Although there were a few successive synergistic organocatalysis systems,[4] it is still of great importance to develop new and simple synergistic small organic molecular catalysis.

Quinoline motif widely exists in pharmaceutical, agrochemical, and advanced material. 2-Alkenylquinoline is one of typical scaffolds such as Montelukast,[5a] Chimanine B,[5b] and so on.[5c-f] Specifically, 2-alkenylquinoline, containing triphenylamine moiety, has good electrochromic properties.[6] Due to the great importance of 2-alkenylquinolines, various methods have been developed to construct this motif, such as the Wittig reactions with expensive 2-quinolinecarboxaldehydes,[7] condensation reactions of 2-methylquinolines with aldehydes or imines,[8] reductive olefinations of quinoline *N*-oxides with olefins,[9] and dehydrogenative olefinations of 2-methylquinolines with alcohols,[10] *etc*. Along these lines, condensation reactions of 2-methylquinolines with aldehydes were the most available method due to the easy accecebility of both substrates. The nucleophilic enamine, catalytically isomerized from 2-methylquioine,[11] proceeds the Knoevenagel condensation with unactivated aldehyde slowly. Thus, all reported transformations required high reaction temperature and/or large excess of aldehydes (Scheme **1a**). With the development of organocatalysis and synergistic catalysis, we have recently suspected that the synergistic catalysis combined two organocatalysts could enable the condensation reaction under a much milder conditions. Herein, we reported a HOAc/1,3-DMBBA (1,3-dimethylbarbituric acid) -catalyzed dehydration reaction system which allows efficent synthesis of various 2-alkenylquinolines from 2-methylquinolines and aldehydes (Scheme **1b**). This protocol involving cascade Knoevenagel condensation followed by Micheal addition and retra-Micheal addition gave the desired product in good to excellent yield with water as the sole byproduct.

Scheme 1. Synthesis of 2-alkenylquinolines from 2-methylquinolines and aldehydes

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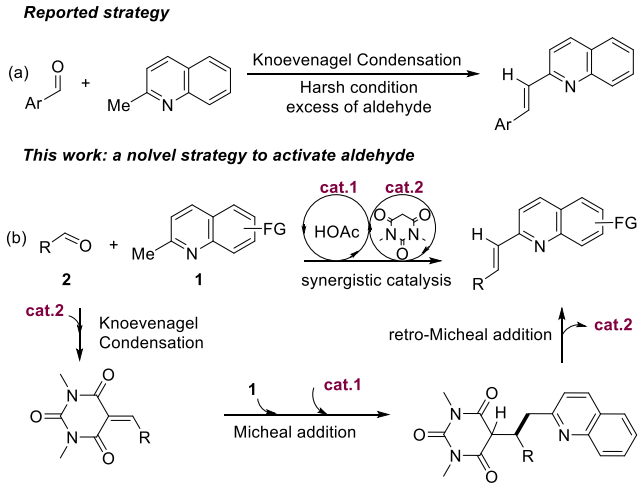
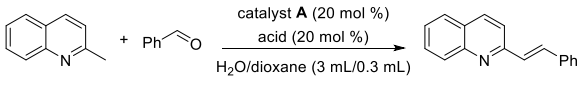
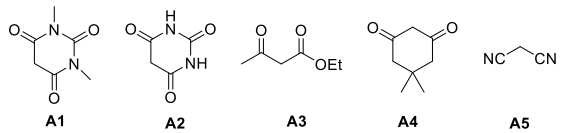


2-Methylquinoline (**1a**) and benzaldehyde (**2a**) were chosen as the model substrates for this investigation, and the results were shown in Table 1. In our initial studies, we found the reaction proceeded in low efficiency under one organocatalyst or without catalyst (Table 1, entries 1-5). To our delight, the reaction yield improved dramatically to 95% in the presence of 20 mol % HOAc and 1,3-DMBBA (Table 1, entry 6). Encouraged by this result, we screened various Bronsted acids (TFA, HCl, $HClO_4$, TsOH), and found that the yields ranged from 68% to 84% (Table 1, entries 7-10). Then, other active methylene compounds (**A2**-**A5**) were used together with HOAc to catalyze this transformation. The results showed that 1,3-DMBBA was the most active catalyst for this reaction (Table 1, entries 11-14). Moreover, the yields decreased with the reduction of the catalyst or acid loading (Table 1, entries 15-16). When we used water as the single solvent, the yield was reduced to 25% (Table 1, entry 17). A gram-scale reaction was performed, and the yield was also satisfactory (Table 1, entry 18).

Table 1. Optimization of the reaction conditions [a]





Entry	Catalyst	Acid	Yield [%]
1	**A1** (20)	--	19
2	--	HOAc (20)	14
3	--	TFA (20)	16
4	--	TsOH (20)	12
5	--	--	trace
6	**A1** (20)	HOAc (20)	95
7	**A1** (20)	TFA (20)	76
8	**A1** (20)	HCl (20)	74
9	**A1** (20)	$HClO_4$ (20)	68
10	**A1** (20)	TsOH (20)	84
11	**A2** (20)	HOAc (20)	13
12	**A3** (20)	HOAc (20)	10
13	**A4** (20)	HOAc (20)	20
14	**A5** (20)	HOAc (20)	39
15	**A1** (10)	HOAc (20)	65
16	**A1** (20)	HOAc (10)	81
17[b]	**A1** (20)	HOAc (20)	25
18[c]	**A1** (20)	HOAc (20)	84

[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (0-20 mol %), acid (0-20 mol %) in H_2O (3.0 mL) and dioxane (0.3 mL) at 60 °C for 24 h. Isolated yield. [b] Water was used as the single solvent. [c] A gram-scale reaction was performed with **1a** (10 mmol), **2a** (10 mmol), 1,3-DMBBA (20 mol%), HOAc (20 mol%), H_2O (40.0 mL), dioxane (4.0 mL), at 60 °C for 24 h.

With the optimized reaction conditions in hand, we firstly studied the scope of methylazaarenes and the results were summarized in Scheme 2. Various 2-methylquinolines bearing different substituents on the aromatic ring such as methyl, methoxyl, fluoro, chloro and bromo were transformed into the 2-alkenylated quinolines in good to excellent yields (Scheme 2, **3aa**-**3ja**). When 1-methylisoquinoline was employed in the reaction, the corresponding product was obtained in 62% yield (Scheme 2, **3ka**). In addition, 2-methylquinoxaline was a suitable substrate for this transformation, albeit in a low yield of desired product **3la**. However, the method was not suitable for 2-methylquinoline with strong electron-withdrawing groups (CF_3, NO_2). 2-Methyl pyridine derivatives were not compatible with the present system.

Scheme 2. Substrate scope of various methylazaarenes [a]

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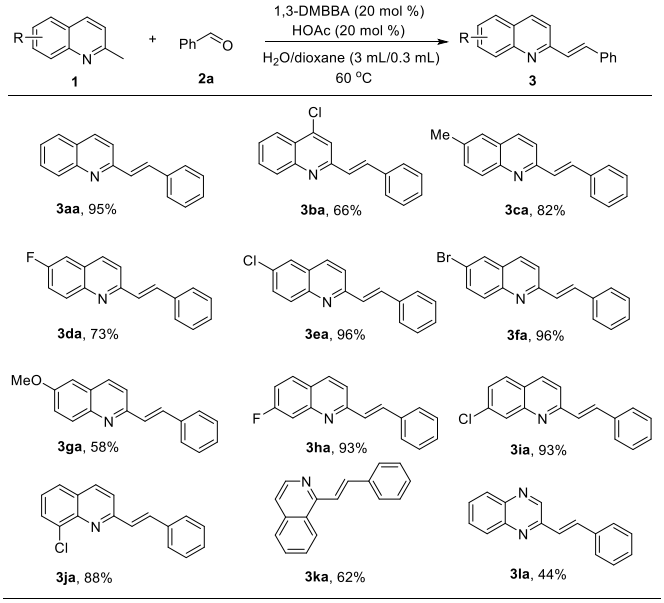
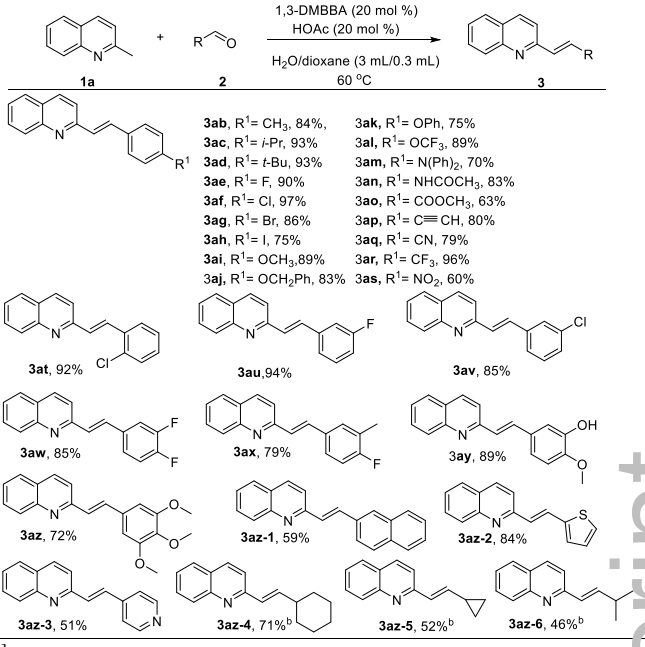


[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), 1,3-DMBBA (20 mol %), HOAc (20 mol %), H_2O (3.0 mL), dioxane (0.3 mL), at 60 °C for 24 h. Isolated yields.



[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), 1,3-DMBBA (20 mol %), HOAc (20 mol %), H_2O (3.0 mL), dioxane (0.3 mL), at 60 °C for 24 h. Isolated yields. [b]1 mmol aldehyde was used.

The reaction scope with respect to aldehydes was next examined (Scheme 3). Substituted benzaldehydes bearing alkyl substituents at the *para* position provided the target products **3ab**, **3ac** and **3ad** in 84%, 93% and 93% yields, respectively. Halogen functional groups (F, Cl, Br, I) were well tolerated to give the corresponding products in good yields (Scheme 3, **3ae**-**3ah**). Furthermore, strong electron-donating and electron-withdrawing groups at the *para* position could also be used to afford the desired products, with the yields ranged from 70% to 89% (Scheme 3, **3ai**-**3am**, **3ar**-**3as**). To our delight, some sensitive groups such as amide, ester, alkynyl and nitrile were all compatible in the present system (Scheme 3, **3an**-**3aq**). In addition, this alkenylation protocol was also applied to *ortho*-, *meta*- and multi-substituted benzaldehydes affording the target products in good to excellent yields (Scheme 3, **3at**-**3az**). Gratifyingly, other aromatic and heteromatic aldehydes including 2-naphthaldehyde, thiophene-2-carboxaldehyde and 4-pyridinecarboxaldehyde were converted into corresponding products in acceptable yields (Scheme 3, **3az-1**-**3az**-**3**). Finally, when aliphatic aldehydes were used as the substrates, moderate yields were generally obtained even with excessive aldehydes (Scheme 3, **3az-4**-**3az-6**).

Scheme 3. Substrate scope of various aldehydes [a]

To gain some mechanistic information, we conducted several control experiments (Scheme 4). With the treatment of 1, 3-DMBBA and benzaldehyde in the presence of 20 mol% HOAc, the condensation product **4** was obtained in 79% yield. While the yield was 80% in the absence of HOAc [Eq. (1)]. Those results reveal that **4** may be an intermediate and its formation is not catalyzed by HOAc. It was found that 57% yield of **5** and 20% yield of **3aa** were obtained when the reaction was carried with **4** and 2-methylquinolines in the present of HOAc. While the yields of **5** and **3aa** were obviously decreased when the same reaciton occurred in the absence of HOAc [Eq. (2)]. Those results suggested that HOAc played a key role in the Michael addition process. Furthermore, compound **5** could transform to product **3aa** under the standard reaction conditions [Eq. (3)], which indicated that compound **5** could probably be the intermediate of this transformation. On the basis of the results described above and literatures, a plausible mechanism was proposed. Firstly, 2-methylquinolines is isomerized into its more nucleophilic enamine isomer **A** by Brønsted acid-promoted.[11] At the same time, **2a** and 1,3-DMBBA undergo Knoevenagel condensation to produce intermediate **4**. The intermediate **A** proceeds through a Michael addition to intermediate **4** to form intermediate **5**, which dissociates into 1,3-DMBBA and the product **3aa** by a retro-Michael addition.

Scheme 4. Control experiments and Plausible reaction mechanism

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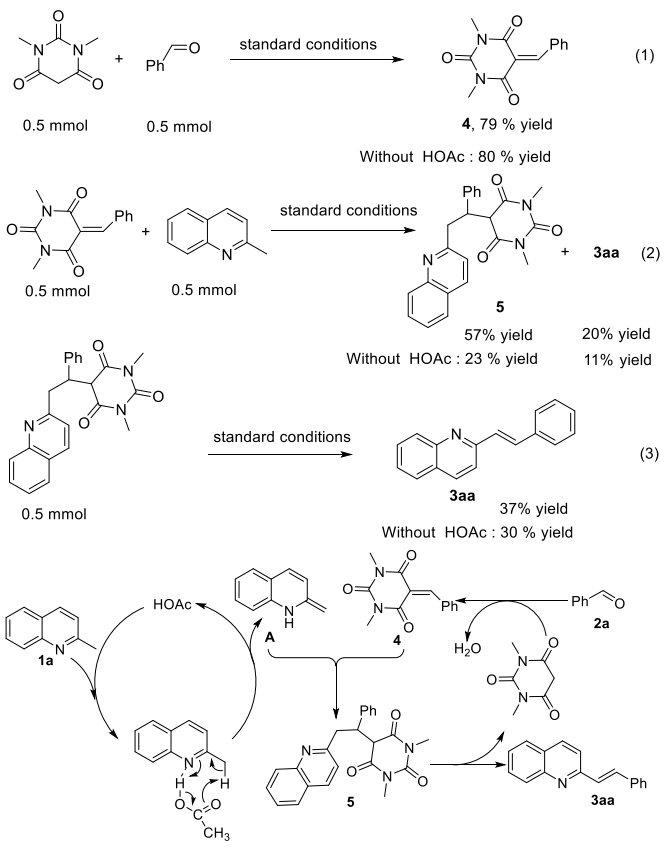

In summary, we have successfully combined two organocatalysis strategies, in which the HOAc activated of 2-methylquinolines and 1,3-DMBBA condensated with aldehydes. The synergistic catalysis provided a novel concept to aceess various 2-alkenylquinolines in good to excellent yields from cheap and commerically available starting materials. The attraction of those transformations included available materials, non-toxic catalysts, mild conditions, simple operation and good functional tolerance.

Experimental Section

General Procedure for the Synthesis of Product 3

2-methylquinoline **1** (0.5 mmol), aldehyde (0.5 mmol), HOAc (20 mol %), 1,3-DMBBA (20 mol %), H_2O (3.0 mL), dioxane (0.3 mL), were added to a 25 mL tube with magnetic stirrer bar. The reaction mixture was stirred at 60°C (oil bath temperature) for 24 h. After the reaction was finished (monitored by TLC), the mixture was cooled to room temperature, quenched with solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by column chromatography (EtOAc/hexanes) on silica gel.

Acknowledgements

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References

[1] For recent reviews, see e.g.: a) H. Guo, Y. C. Fan, Z. Sun, Y. Wu, O. Kwon, *Chem. Rev*. **2018**, *118*, 10049-10293; b) Y. Qin, L. Zhu, S. Luo, *Chem. Rev*. **2017**, *117*, 9433-19520; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304-308; d) A.-N. R. Alba, X. Companyó, R. Rios, *Chem. Soc. Rev*. **2010**, *39*, 2018-2033; e) G. Fiorani, W. Guo, A. W. Kleij, *Green Chem*. **2015**, *17*, 1375-1389.

[2] For recent reviews, see e.g.: a) L. Omann, C. D. F. Königs, H. F. T. Klare, M. Oestreich, *Acc. Chem. Res*. **2017**, *50*, 1258-1269; b) P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 1-24; c) J. Fu, X. Huo, B. Lia, W. Zhang, *Org. Biomol. Chem*. **2017**, *15*, 9747-9759; d) S. M. Inamdar, V. S. Shinde, N. T. Patil, *Org. Biomol. Chem*. **2015**, *13*, 8116-8162.

[3] a) F. A. Cruz, V. M. Dong, *J. Am. Chem. Soc*. **2017**, *139*, 1029-1032; b) L. A. Leth, F. Glaus, M. Meazza, L. Fu, M. K. Thøgersen, E. A. Bitsch, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2016**, *55*, 15272-15276; c) S. Zhu, Q. Zhang, K. Chen, H. Jiang, *Angew. Chem. Int. Ed.* **2015**, *54*, 9414-9418; d) L. Wei, S.-M. Xu, Q. Zhu, C. Che, C.-J. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 12312-12316; e) S. Yang, K.-H. Rui, X.-Y. Tang, Q. Xu, M. Shi, *J. Am. Chem. Soc*. **2017**, *139*, 5957-5964; f) M. Michalska, O. Songis, C. Taillier, S. P. Bew, V. Dalla, *Adv. Synth. Catal*. **2014**, *356*, 2040-2050; g) L. Wei, L. Xiao, C.-J. Wang, *Adv. Synth. Catal*. **2018**, *360*, 4715-4719; h) X. Chen, H. Zhao, C. Chen, H. Jiang, M. Zhang, *Chem. Commun*. **2018**, *54*, 9087-9090.

[4] a) Y. Ni, H. Zuo, H. Yu, Y. Wu, F. Zhong, *Org. Lett*. **2018**, *20*, 5899-5904; b) J. Xu, X. Chen, M. Wang, P. Zheng, B.-A. Song, Y. R. Chi, *Angew. Chem. Int. Ed.* **2015**, *54*, 5161-5165.

[5] a) M. L. Belley, S. Leger, M. Labelle, P. Roy, Y. B. Xiang, D. Guay, U.S. Patent Appl. US 5565473,1996; b) J. P. Michael, *Nat. Prod. Rep*. **2005**, *22*, 627-646; c) X.-Q. Wang, C.-L. Xia, S.-B. Chen, J.-H. Tan, T.-M. Ou, S.-L. Huang, D. Li, L.-Q. Gu, Z.-S. Huang, *Eur. J. Med. Chem*. **2015**, *89*, 349-361; d) W. Cieslik , R. Musiol, J. E. Nycz, J. Jampilek, M. Vejsova, M. Wolff, B. Machura, J. Polanski, *Bioorg. Med. Chem*. **2012**, *20* 6960-6968; e) J. Polanski, F. Zouhiri, L. Jeanson, D. Desmaele, J. d'Angelo, J.-F. Mouscadet, R. Gieleciak, J. Gasteiger, M. L. Bret, *J. Med. Chem*. **2002**, *45*, 4647-4654; f) C.-H. Tseng, Y.-L. Chen, C.-Y. Hsu, T.-C. Chen, C.-M. Cheng, H.-C. Tso, Y.-J. Lu, C.-C. Tzeng, *Eur. J. Med. Chem*. **2013**, *59*, 274-282.

[6] a) S.-H. Kim, J.-H. Ryu, H.-J. Choi, H.-S. Kim, *Dyes Pigments* **2005**, *64*, 279-281; b) Y. Yue, M. Yu, L. Zhu, *J. Chem. Res*. **2009**, 427-429.

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10.1002/adsc.201900351

[7]M. A. Fakhfakh, X. Franck, A. Fournet, R. Hocquemiller, B. Figadère, *Synth. Commun*. **2002**, *32*, 2863-2875.

[8] a) Z. Jamal, Y.-C. Teo, *Synlett* **2014**, *25*, 2049-2053; b) Z. Jamal, Y.-C. Teo, G. S. Lim, *Tetrahedron* **2016**, *72*, 2132-2138; c) S. Fu, L. Wang, H. Dong, J. Yu, L. Xu, J. Xiao, *Tetrahedron Lett*. **2016**, *57*, 4533-4536; d) D. Pi, K. Jiang, H. Zhou, Y. Sui, Y. Uozumi, K. Zou, *RSC Adv*. **2014**, *4*, 57875-57884; e) Y. Yan, K. Xu, Y. Fang, Z. Wang, *J. Org. Chem*. **2011**, *76*, 6849-6855.

[9] a) Z. Zhang, C. Pi, H. Tong, X. Cui, Y. Wu, *Org. Lett*. **2017**, *19*, 440-443; b) H. Xia, Y. Liu, P. Zhao, S. Gou, J. Wang, *Org. Lett*. **2016**, *18*, 1796-1799.

[10] a) G. Zhang, T. Irrgang, T. Dietel, F. Kallmeier, R. Kempe, *Angew. Chem. Int. Ed*. **2018**, *57*, 9131-9135; b) M. K. Barman, S. Waiba, B. Maji, A*ngew. Chem. Int. Ed.* **2018**, *57*, 9126-9130.

[11] a) F.-F. Wang, C.-P. Luo, G. Deng, L. Yang, *Green Chem*. **2014**, *16*, 2428-2431; b) Z. Zhu, P. Bai, Z.-Z. Huang, *Org. Lett*. **2014**, *16*, 4881-4883; c) H. Xie, Y. Liao, S. Chen, Y. Chen, G.-J. Deng, *Org. Biomol. Chem*. **2015**, *13*, 6944-6948; d) B. Qian, D. Shi, L. Yang, H. Huang, *Adv. Synth. Catal*. **2012**, *354*, 2146-2150; e) H. Xie, J. Cai, Z. Wang, H. Huang, G.-J. Deng, *Org. Lett*. **2016**, *18*, 2196-2199; f) F. Xiao, S. Chen, Y. Chen, H. Huang, G.-J. Deng, *Chem. Commun*. **2015**, *51*, 652-654; g) H. Huang, Q. Wang, Z. Xu, G.-J. Deng, *Adv. Synth. Catal*. **2019**, *361*, 591-596; h) F. Xiao, C. Liu, S. Yuan, H. Huang, G.-J. Deng, *J. Org. Chem*. **2018**, *83*, 10420-10429.

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UPDATE

Direct Alkenylation of 2-Methylquinolines with Aldehydes through Synergistic Catalysis of 1,3-Dimethylbarbituric Acid and HOAc

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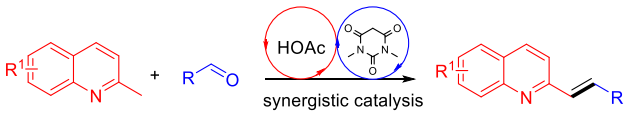

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