

Efficient synthesis of 3-substituted 2,3-dihydroquinolin-4-ones using a one-pot sequential multi-catalytic process: Pd-catalyzed allylic amination–thiazolium salt-catalyzed Stetter reaction cascade

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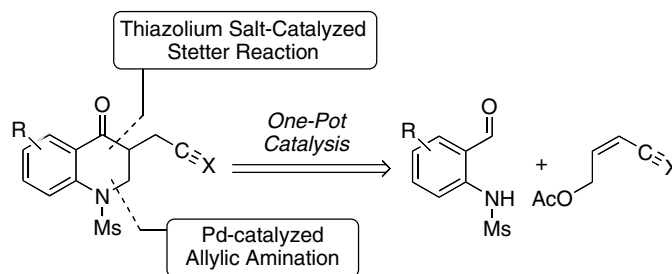
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Abstract—We developed an efficient method for the synthesis of 3-substituted 2,3-dihydroquinolin-4-ones using a one-pot sequential multi-catalytic process: Pd-catalyzed allylic amination–thiazolium salt-catalyzed Stetter reaction cascade. Measurement of the initial rate of the developed sequential process revealed a significant increase in the reaction rate of the Stetter reaction in the presence of Pd(OAc)₂ and AcOH·*i*-Pr₂NEt, the constituents of the first Pd catalysis.
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Hydroquinolines are ubiquitous structural motifs in various natural products that exhibit a variety of biological activities.¹ From a synthetic point of view, 2,3-dihydroquinolin-4-ones are versatile intermediates for the synthesis of functionalized hydroquinolines. Several dihydroquinolinones are utilized as the key intermediate for the synthesis of natural products containing a hydroquinoline core such as martinelline and martinelic acid.^{2,3} A thiazolium salt-catalyzed intramolecular Stetter reaction is one of the most useful methods for constructing substituted dihydroquinolinones.⁴ Substrates for the intramolecular Stetter reaction can be efficiently prepared using Pd-catalyzed allylic amination of γ -acet-

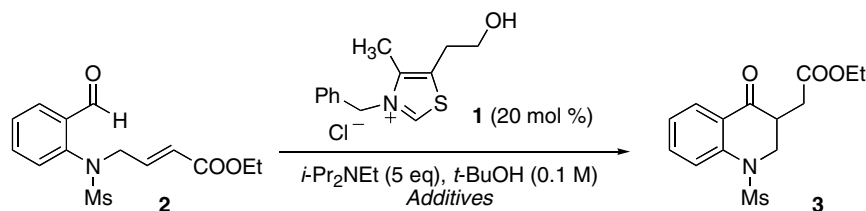
oxy α,β -unsaturated carbonyl compounds with 2-amino-benzaldehyde derivatives.⁵ If these two reactions can be performed without interfering with the individual catalytic processes, functionalized dihydroquinolinones are directly obtained in a single-pot reaction (Scheme 1). The combination of different types of catalysis in a single reaction process increases synthetic efficiency and helps to reduce waste.^{6,7} In addition, this type of sequential catalysis is quite attractive if the first and/or second reactions beneficially affect on the other catalysis.⁸ Herein, we report an efficient method for the synthesis of 3-substituted 2,3-dihydroquinolin-4-ones using a one-pot sequential multi-catalytic process.



Scheme 1. Synthetic strategy.

Keywords: Pd-catalyzed allylic amination; Sequential multi-catalytic process; Stetter reaction; 3-Substituted 2,3-dihydroquinolin-4-ones.

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Table 1. Preliminary experiments for the Stetter reaction of **2**

Entry	Additives	Temperature (°C)	Time (h)	Yield ^a (%)
1	—	30	3	58
2	Pd(OAc) ₂ (5 mol %)	30	3	67
3	Ph ₃ P (12 mol %)	30	3	72
4	AcOH (1.0 equiv)	30	3	88
5	Pd(OAc) ₂ (5 mol %), PPh ₃ (12 mol %)	30	3	82
6	Pd(OAc) ₂ (5 mol %), PPh ₃ (12 mol %), AcOH (1.0 equiv)	30	3	84
7	Pd(OAc) ₂ (5 mol %), PPh ₃ (12 mol %), AcOH (1.0 equiv)	50	3	100 (99) ^b

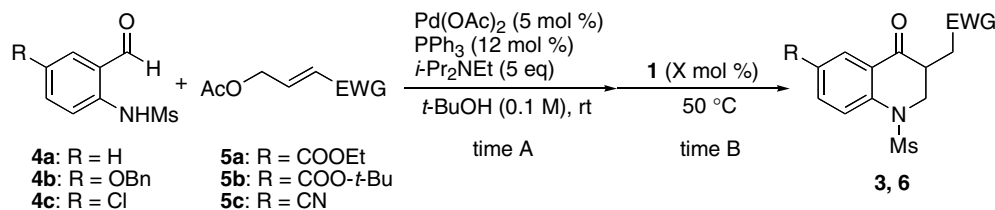
^a Determined by ¹H NMR analysis of the crude product.

^b Isolated yield.

The key to success of the target process is the compatibility of the second catalysis with the conditions of the first Pd catalysis. Therefore, we first performed experiments to examine the influence of the constituents of the first reaction on the second catalysis (Table 1). Using 20 mol % of thiazolium salt **1**, an intramolecular Stetter reaction of **2** was investigated as a model reaction. In the absence of additives, the reaction proceeded at 30 °C to give the dihydroquinolinone **3** in 58% yield. Interestingly, there was a significant increase in the chemical yield of **3** when the reaction was performed in the presence of 5 mol % of Pd(OAc)₂, triphenylphosphine (12 mol %), and acetic acid (1 equiv). The positive effect on the reactivity was also observed in the reaction conditions that included all of the reagents for the first reaction. The cyclic product **3** was obtained in quantitative yield when the reaction was performed at 50 °C. This finding suggests that beneficial modifications of the second catalytic process were achieved by the constituents of the first Pd catalysis, producing a more suitable condition for the second intramolecular Stetter reaction.

Based on the preliminary experiments, we examined a one-pot sequential multi-catalytic process. After completion of the Pd-catalyzed allylic amination of aldehyde **4a** with γ -acetoxy α,β -unsaturated ester **5a**, 20 mol % of **1** was directly added to the reaction mixture and the resulting mixture was stirred at 50 °C (a two-step procedure⁹) (Table 2). As expected, the desired sequential process proceeded efficiently to afford **3** in 97% yield (entry 1). Substrate scope was examined using 5 mol % of Pd catalyst and 10–30 mol % of **1**. Nucleophiles with an electron-donating substituent and an electron-withdrawing substituent on the aromatic ring, were applicable to this reaction process, affording the corresponding product in excellent yield (entries 3 and 4). In contrast to that of γ -acetoxy α,β -unsaturated esters, a reaction using γ -acetoxy α,β -unsaturated nitrile gave complex reaction mixtures at the allylic amination stage (entry 6).

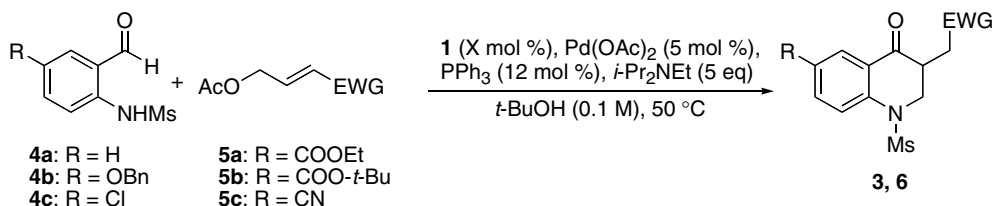
The present one-pot sequential multi-catalytic process was successful even when both catalysts coexisted in the reaction mixture at the first stage of the reaction

Table 2. One-pot sequential multi-catalytic process: two-step procedure

Entry	Aldehyde	Acetate	1 (mol %)	Time A (h)	Time B (h)	Product	Yield ^a (%)
1	4a	5a	20	6	12	3	97
2 ^b	4a	5a	10	6	72	3	97
3	4b	5a	30	16	24	6ba	98
4	4c	5a	30	16	24	6ca	94
5	4a	5b	20	6	12	6ab	99
6	4a	5c	30	12	—	6ac	Messy

^a Isolated yield.

^b The second step was performed at 70 °C.

Table 3. One-pot sequential multi-catalytic process: one-step procedure

Entry	Aldehyde	Acetate	1 (mol %)	Time (h)	Product	Yield ^a (%)
1	4a	5a	20	12	3	98
2	4b	5a	30	24	6ba	No reaction
3	4c	5a	30	24	6ca	No reaction
4	4a	5b	20	12	6ab	99
5	4a	5c	30	12	6ac	99

^a Isolated yield.

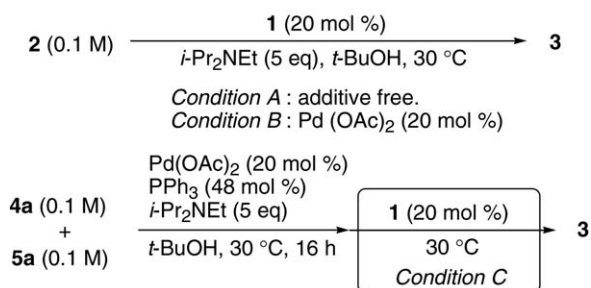
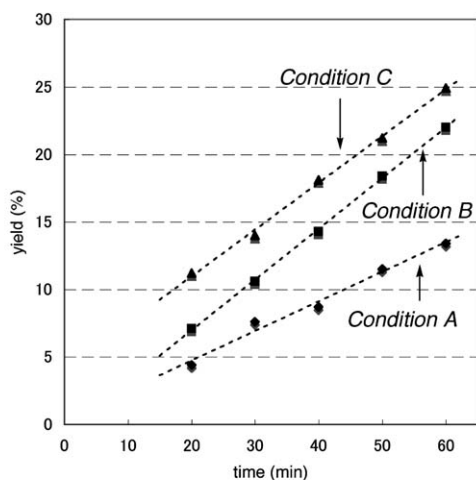
(a one-step procedure¹⁰) (Table 3). Aldehyde **4a** and γ -acetoxy α,β -unsaturated ester **5a** were dissolved in *tert*-BuOH, and the solution was heated at 50 °C in the presence of both catalysts, giving **3** in 98% yield (entry 1). Unexpectedly, the first allylic amination did not proceed at all when aldehydes **4b** and **4c** were used as the nucleophile. On the other hand, a reaction with γ -acetoxy α,β -unsaturated nitrile **5c** proceeded smoothly to afford the corresponding product in 99% yield using the one-step procedure (entry 5). This result might be due to rapid consumption of the γ -amino α,β -unsaturated nitrile intermediate, compared to that of the two-step procedure.

As shown in Table 1, there was a significant increase in the chemical yield of **3** in the presence of a catalytic amount of Pd(OAc)₂ and other constituents of the first Pd catalysis. To quantitatively evaluate the increased reactivity of the Stetter reaction, the initial rate of the developed sequential multi-catalytic process was measured (Fig. 1).¹¹ Compared with the control reaction (condition A: 3.65×10^{-4} M/s), the reaction rate was increased in the presence of 20 mol % of Pd(OAc)₂ (condition B: 6.27×10^{-4} M/s). In particular, the similar rate acceleration which was observed in the one-pot multi-catalytic process (condition C: 5.77×10^{-4} M/s) is to be noted. The mode of rate acceleration by Pd(OAc)₂ is not clear. The fact that the addition of other metal acetates also increases the reaction rate, suggests that the Lewis acidic property of the metal species is related to the rate acceleration¹¹: LiOAc (20 mol %): 5.92×10^{-4} M/s, Zn(OAc)₂ (20 mol %): 5.95×10^{-4} M/s, In(OAc)₃ (20 mol %): 4.93×10^{-4} M/s, Yb(OAc)₃·4H₂O (20 mol %): 7.25×10^{-4} M/s. In addition, the reaction rate was increased in the presence of 1 equiv of acetic acid (9.81×10^{-4} M/s). In this case, ammonium salt (AcOH·*i*-Pr₂NEt) would function as Brønsted acid and accelerate the reaction. These findings demonstrate the synthetic utility of the developed sequential multi-catalytic process, and provide useful information for designing a new catalyst system for the Stetter reaction.^{12,13}

In conclusion, we developed an efficient method for the synthesis of 3-substituted 2,3-dihydroquinolin-4-ones using a one-pot sequential catalysis: Pd-catalyzed allylic substitution–thiazolium salt-catalyzed Stetter reaction cascade. Measurement of the initial rate of the developed process revealed a significant increase in the reaction rate of the Stetter reaction in the presence of Pd(OAc)₂ and AcOH·*i*-Pr₂NEt, the constituents of the first Pd catalysis.

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**Figure 1.** Measurement of initial rate.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.095.

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- General procedure for the two-step procedure: To a stirred solution of Pd(OAc)₂ (2.51 mg, 0.0112 mmol), PPh₃ (7.04 mg, 0.0268 mmol), **5a** (38.5 mg, 0.224 mmol), and **4a** (53.5 mg, 0.268 mmol) in *t*-BuOH (2.2 mL) at room temperature was added *i*-Pr₂NEt (184 μ L, 1.12 mmol) under an argon atmosphere. After 6 h, thiazolium salt **1** (12.1 mg, 0.0448 mmol) was added to the reaction, and the mixture was stirred for 12 h at 50 °C. The reaction mixture was diluted with ethyl acetate, and washed with saturated aqueous NH₄Cl, water, then dried over Na₂SO₄. After concentration in vacuo, the residue was purified by flash chromatography (SiO₂, hexane/ethyl acetate 30/1) to give **3** as yellow oil: 67.6 mg (97%). IR (neat): ν = 3022, 2980, 2932, 1728, 1693, 1600, 1478, 1457, 1353, 1299, 1257, 1220, 1157, 964, 768 cm⁻¹; ¹H NMR (CDCl₃): δ = 1.29 (t, J = 7.2 Hz, 3H), 2.58 (dd, J = 7.6 Hz, 17.2 Hz, 1H), 2.91 (dd, J = 4.8 Hz, 17.2 Hz, 1H), 3.12 (s, 3H), 3.30 (dddd, J = 4.8 Hz, 4.8 Hz, 7.6 Hz, 12.4 Hz, 1H), 3.81 (dd, J = 12.4 Hz, 13.2 Hz, 1H), 4.19 (dq, J = 2.4 Hz, 7.2 Hz, 2H), 4.50 (dd, J = 4.8 Hz, 13.2 Hz, 1H), 7.22–7.26 (m, 1H), 7.54–7.58 (m, 1H), 7.75–7.78 (m, 1H), 8.05–8.07 (m, 1H); ¹³C NMR (CDCl₃): δ = 14.1, 31.7, 39.9, 43.2, 49.7, 61.1, 121.0, 123.8, 124.6, 128.6, 135.0, 142.3, 171.1, 193.3; FAB-LRMS: m/z 312 (MH⁺).
- General procedure for the one-step procedure: To a stirred solution of Pd(OAc)₂ (1.21 mg, 0.0054 mmol), PPh₃ (3.40 mg, 0.0130 mmol), **4a** (18.6 mg, 0.108 mmol), **5a** (25.8 mg, 0.130 mmol), and thiazolium salt **1** (5.83 mg, 0.0216 mmol) in *t*-BuOH (1.1 mL) was added *i*-Pr₂NEt (89 μ L, 0.54 mmol), and the mixture was heated to 50 °C. After 12 h, the reaction mixture was diluted with ethyl acetate, and washed with saturated aqueous NH₄Cl, water, then dried over Na₂SO₄. After concentration in vacuo, the residue was purified by flash chromatography (SiO₂, hexane/ethyl acetate 30/1) to give **3** as yellow oil: 33.3 mg (99%).
- See [Supplementary data](#) for detail.
- To the best of our knowledge, there is no report on Lewis acid acceleration of the Stetter reaction.
- Very interestingly, faster reaction rate was observed using less amount of Pd(OAc)₂ as an additive: 5 mol %: 1.67×10^{-3} M/s, 10 mol %: 8.22×10^{-4} M/s, 20 mol %: 6.27×10^{-4} M/s, 30 mol %: 3.73×10^{-4} M/s. At the present stage, it is difficult to give a reasonable explanation for these experimental results. However, it can be emphasized that catalytic amount of Pd(OAc)₂ increases the reaction rate of the Stetter reaction. See [Supplementary data](#) for detail.