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Two-Step Continuous-Flow Synthesis of Fungicide Metalaxyl through Catalytic C–N Bond-Formation Processes

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Abstract: Metalaxyl, an acylalanine fungicide, was synthesized through catalytic continuous sequentialflow reactions. Commonly used syntheses of this compound use batch systems and suffer from problems such as coproduction of halogen-containing by-products derived from acyl and alkyl halides in the substitution reactions of 2,6-dimethylaniline. To minimize waste and enhance efficiency, a halidefree approach including two continuous-flow catalytic processes, heterogeneous Pt-catalyzed reductive alkylation and homogeneous acid-catalyzed amidation with an acid anhydride, was developed. Systematic examination of the two reactions in flow mode enabled a high-yielding, two-step sequential continuous-flow process to be achieved.

Keywords: sequential continuous-flow; reductive alkylation; heterogeneous catalyst; amidation; metalaxyl Although a highly controversial issue, the use of pesticides is still important for securing efficient and reliable supplies of crops and foods worldwide. To reduce the environmental impact associated with pesticide use, harmful processes associated with their manufacture must be minimized and efficient technologies in this field are in high demand. A series of acyl alanine-type pesticides such as metalaxyl (1), benalaxyl (2), furalaxyl (3), and ofurace (4) are common, commercially available phenylamide fungicides (PAFs; Scheme 1(a)).^[1] PAFs affect mitosis and cell division in fungi, and are widely used on a preventive basis for plant diseases. An easily visualized and reliable method for preparing these PAFs as racemates includes alkylation and acylation (amidation) of the nitrogen atom of 2,6-dimethylaniline (5), as shown in Scheme 1(b).^[2] Typical methods that are used for these two transformations require organic halides with stoichiometric amounts of base; however, such approaches produce large amounts of waste organic halides. The structural features of these PAFs demand harsh conditions to achieve substitution reactions at the nitrogen atom of sterically hindered 2,6-dimethylaniline. Likewise, the conjunction of the two frag-





Scheme 1. (a) Structures of commercial PAFs. (b) Typical synthetic route to PAFs. (c) This work.

ments requires appropriate separation and purification steps to remove by-products. Such waste-generating processes should be avoided in industry to decrease the amount of environmental pollutants. To address these issues, the use of catalytic processes with environmentally benign reagents for the two modifications on the nitrogen atom is highly desirable.

We previously reported a continuous-flow process of reductive amination of carbonyl compounds with hydrogen as a surrogate for a conventional substitution reaction on the amine.^[3,4] In this context, and to demonstrate the efficiency of the flow reductive amination as a waste-free N-alkylation process for the synthesis of useful compounds, we designed a novel two-step sequential-flow synthesis of metalaxyl, including catalytic amidation as a second step (Scheme 1(c)). Multistep continuous-flow synthesis is now widely recognized as an enabling technology for the synthesis of fine chemicals, pharmaceuticals, and agrochemicals,^[5] with many reports and reviews addressing its applications.^[6,7] The true potential of continuous-flow synthesis as a next-generation technology for chemical processes can be met when a flow reaction is performed using fully catalytic processes with high productivity.^[8] In this paper, we describe the synthesis of metalaxyl in a two-step catalytic sequential-flow manner.

We first investigated reductive alkylation of 2,6dimethylaniline (5) with methyl pyruvate (6) to construct N-(2,6-xylyl)alanine methyl ester (7), the common intermediate of PAFs. Based on our experience gained in the previous studies on reductive C-N bond formation, we first chose a heterogeneous platinum catalyst (Pt/C) as a candidate for the reaction. Our basic continuous-flow hydrogenation system is illustrated in Scheme 2. The system included Reservoir A, containing a solution of 5 and 6 in toluene, which was pumped into a 10 mm × 100 mm stainless-steel column reactor equipped with a double-inlet-type column head. A back-pressure regulator (BPR) was included in the outlet line to maintain the pressure of the reactor at 0.1-0.5 MPa. Although consumption of **6** was rapid under the conditions given in Table 1, Entry 1, conversion of 5 and the yield of the desired product 7 were poor (Entries 1 and 2). The use of Pt/ Al_2O_3 as a catalyst gave similar results (Entry 3). The main product obtained by catalysis with Pt/C under the conditions given in Entry 2 was found to be methyl lactate 8 (>95% based on 6), a reduced alcohol product of pyruvate 6. This indicated that hydrogenation of the carbonyl group in methyl pyruvate (6) was faster than the imine or its intermediate formation by the reaction between 6 and aniline 5 due to the steric hindrance of 5. To suppress the rapid hydrogenation of the activated ketone moiety, we investigated the use of poisoned catalysts and found that a commercially available Pt on sulfided carbon (Pt/s-C) provided a moderate yield, although lactate 8 was still seen in the output (Entry 4). Notably, although highpressure conditions such as 5 to 8 MPa were normally required to accomplish the reaction in conventional batch systems,^[9] lower back pressure of 0.2 MPaG was sufficient for the present flow system. We further investigated flow conditions to attain high yield and to gain more information on catalyst performance to increase productivity. A high Pt loading slightly improved the yield, and the use of 2 equiv. of pyruvate 6, to accelerate the reaction between 5 and 6, gave the desired N-(2,6-xylyl)alanine in 93% yield (Entries 5 and 6). With the same Pt loading, 0.2 mmol in



Scheme 2. Reaction setup for continuous-flow reductive alkylation.

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Entry	Catalyst ^[a]	5 /6 (M/M)	SVmol (h^{-1})	Conv. 5 (%) ^[b]	Yield 7 (%) ^[b]
1	Pt/C	0.1/0.12	10	6	<5
2	Pt/C ^[c]	0.1/0.2	6	17	10
3	Pt/Al ₂ O ₃	0.1/0.12	10	6	< 5
4 ^[d]	Pt/s-C	0.1/0.12	10	55	51
5	Pt/s-C	0.1/0.12	10	74	73
6	$Pt/s-C^{c}$	0.1/0.2	6	94	93

Table 1. Continuous-flow reductive alkylation of 5.

^[a] 0.12 mmol Pt was used.

^[b] Determined using GC analysis.

^[c] 0.2 mmol Pt was used.

^[d] Without back pressure.

reactor **I**, we examined the effect of substrate concentration to attain high productivity. The mole ratio of the two reactants and the flow rate of the solution were fixed at 5/6 = 1:2 and 0.2 mL/min, respectively, and the yields of the desired 7 are plotted in Figure 1 as a function of substance amount (moles)-based space velocity (SVmol), meaning the amount of 5 supplied for Pt in a reactor in an hour. Around 90% yields were



Figure 1. Dependence of the yield on SVmol value; *Conditions*: Pt/s-C, 0.2 mmol (Pt); **5**, 0.1 M; **6**, 0.2 M; $v_{sub}=0.2$ mL/min, Reactor Temp., 120 °C; Back pressure, 0.2 MPaG. The open circle indicates the result using **5**/6=1:1.2 solution (Table 1, Entry 5).



Figure 2. Long-run experiment on reductive alkylation; *Conditions*: Pt/s-C, 0.12 mmol (Pt); **5**, 0.1 M; **6**, 0.2 M; $v_{sub} = 0.2 \text{ mL/min}$, Reactor temp., 120 °C; Back pressure, 0.2 MPaG.

an acylating agent and surveyed the use of acid catalysis for this amidation. Table 2 summarizes selected results of batch experiments for this catalytic amidation with anhydride **9**. Among the variety of acids studied, solid acids bis(trifluoromethanesulfonyl) imide (Tf_2NH) and $Fe(OTf)_3$ showed promising activities and gave the corresponding amide in 67 and 80% yield, respectively (see also Table S5). Moving on to continuous-flow experiments, we faced an issue of solvent choice; we initially wanted to use a toluene

12.8 g.

solution of 7 in a sequential continuous-flow system. However, requirements of both higher reaction temperature and solubility for Tf_2NH and $Fe(OTf)_3$ prevented the use of toluene as a sole solvent. Furthermore, especially for iron-based Lewis acids, the use of polar solvents proved disappointing and suppressed the reaction. We then examined a range of solvents

maintained from SVmol of 3 to $36 h^{-1}$; even at

 $SVmol = 36 h^{-1}$ using a 0.6 M solution of 5, a yield of

87% was obtained, indicating 6.5 g of N-(2,6-xylyl)

alanine methyl ester 7 was obtained per 1 mmol of Pt within an hour. Higher SVmol conditions using a

0.8 M solution at SVmol = $48 h^{-1}$ strongly affected the

performance of the catalyst, and the yield of 7

decreased to 29%. Further investigations to establish the catalysis turnover were performed in a long-run experiment. Figure 2 shows the change in yield of 7 over the running time. The SVmol value was set to

 10 h^{-1} for this experiment. Yields of 97–94% were

attained in the initial 18-26 h, and the high yields were

maintained for >74 h. In addition, a lead time until reaching a steady state was estimated to be ca. 4 h. The upper scale in Figure 2 indicates the total amount of **5**

supplied per Pt atom in reactor I; the turnover number for Pt with the present catalyst for 0-74 h was

estimated to be 680, based on the average 92% yield. The productivity in this reductive alkylation step during the period of 18-74 h was calculated to be ca.

We then focused on the acylation of N-(2,6-xylyl)

alanine methyl ester 7. We chose the corresponding

acid anhydride, methoxyacetic acid anhydride (9), as

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Me Me 7 1.0	Me NH + N CO_2Me 0 mmol	∎eO2O	Catal Toluc (0.1 3 1	yst ene Me M) M	M ^e O N OMe CO ₂ Me
Entry	Catalyst			Temp./°C	Yield/% ^[a]
1	β-zeolite	200 mg/mm	ol ₇	110	9
2	Y-zeolite	200 mg/mm	ol ₇	110	6
3	$Sc(OTf)_3$	10 mol%		110	22
4	$Fe(OTf)_3$	10 mol%		110	80
5	АсОН	50 mol%		140	30
6	Tf ₂ NH	25 mol%		140	67

 Table 2. Effect of catalyst on amidation.

^[a] Determined using ¹H NMR analysis.

together with Tf₂NH (Table S6) and decided to use odichlorobenzene (o-DCB) as the solvent for 9, which allowed a stable flow to be maintained in the reaction at the required high temperature, and DMF as the solvent for Tf_2NH , to make the solution homogeneous. With these solvents, we examined several continuousflow conditions as illustrated in Scheme 3. Solutions of pure intermediate 7 in toluene and anhydride 9 in o-DCB were separately supplied at flow rates of 0.1 and 0.05 mL/min, respectively, and a Tf₂NH solution in DMF was assembled before mixing and flow onto a reactor heating area. We used a 10 mm × 200 mm stainless-steel plug flow reactor filled with Celite, which provided a higher mixing efficiency than PTEF or SUS coil reactors.^[10] A 97% yield of the desired metalaxyl 1 was determined using ¹H NMR analysis when 1.5 equiv. of anhydride 9 was employed and the reaction was performed at 140 °C. Under these conditions, 25 mol% Tf₂NH was employed for the reaction and the residence time for the Celite-packed reactor



Scheme 3. Continuous-flow catalytic amidation.

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(with a void space for liquid of 7.14 mL) was estimated to be 42 min based on 0.17 mL/min total flow rate.

Finally, we combined the above two flow processes as shown in Scheme 4 to achieve sequential-flow synthesis. A 0.1 M and 0.2 M mixed solution of aniline 5 and pyruvate 6 in Reservoir A was flowed into packed catalyst reactor I of 3% Pt/s-C (Pt: 0.2 mmol) at a flow rate of 0.1 mL/min with hydrogen gas. The outlet flow was cooled to prevent evaporation of the solvent, and passed through a BPR and received in Reservoir **B**. The resulting solution of 7 was pumped into amidation reactor II with the anhydride flow and the Tf₂NH flow. The outlet solution from reactor **II** was cooled in an ice bath and collected. The desired metalaxyl 1 was obtained in 89% yield (¹H NMR) after basic work-up, which corresponds to be 0.14 g/h of productivity. Further purification by column chromatography gave pure 1 in 85% isolated yield.

In conclusion, we have developed a two-step sequential continuous-flow synthesis of phenylalanine fungicide metalaxyl without using organic halides. It was found that Pt on a poisoned carbon support was an efficient catalyst for selective reductive alkylation of sterically hindered 2,6-dimethylaniline with pyruvate under continuous-flow conditions with hydrogen gas.



Scheme 4. Two-step sequential-flow synthesis of metalaxyl (1).

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In the sequential process, we have combined the reductive alkylation process with the amidation process by assembling the first stream with the anhydride and Tf_2NH streams, giving the desired fungicide in high overall yield.

Experimental Section

Continuous-Flow Reductive Alkylation

A $10 \text{ mm} \times 100 \text{ mm}$ stainless-steel column (Reactor I) was packed with heterogeneous Pt catalyst, such as Pt/s-C (3% Pt on sulfided carbon, AC-1304 purchased from N.E. CHEMCAT, 0.12 or 0.2 mmol for Pt) with 2.0-4.1 g of Celite as a diluent. On the head part of the column, a double-inlet-type column head was equipped to charge gas and liquid into the catalyst phase separately. The catalyst reactor was first treated with toluene, and then a stock solution of aniline 5 and methyl pyruvate (6) was flowed through. Reactor I was heated to 110°C with a column heater. During these processes, a BPR was needed to stabilize the pressure at 0.2 MPaG. Hydrogen gas was introduced, and the system was kept at the same pressure. The solution was flowed for 2 h to stabilize the flow system, and then samples were collected at appropriate time intervals. Except for the long-run experiment, at least eight samples were collected to reduce the error margin. The yields and conversions of products and substrates were determined using ¹H NMR spectroscopic (using 1,1,2,2-tetrachloroethane as internal standard) or GC (using mesitylene as internal standard) analyses.

Sequential-Flow Synthesis of Metalaxyl

The first step for the flow synthesis of N-(2,6-xylyl)alanine (7) was conducted as described above, and the resulting solution was collected in a flask (Reservoir **B**) to release H_2 gas. The crude solution in Reservoir B was pumped at a flow rate of 0.1 mL/min, and combined with a stream of methoxyacetic anhydride (0.3 M in o-DCB), provided from another pump at a flow rate of 0.05 mL/min, using a T-shaped connector. A solution of Tf₂NH (0.125 M in DMF) was pumped at a flow rate of 0.02 mL/min and the streams were combined and flowed into a 10 mm × 200 mm stainless-steel column packed with 8.2 g of Celite (Reactor II) heated at 140 °C. The product solution was obtained from the outlet of the ice-cooled loop with a global flow rate of 0.17 mL/min and collected in test tubes kept at room temperature. To check the yield of the product, we usually start a sample collection from an outlet solution after 1 h when the second flow attains a steady state. The yields were determined using ¹H NMR analysis with 1,1,2,2-tetrachloroethane as internal standard after basic workup. Further purification with silica gel column chromatography gave pure metalaxyl.

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References

- [1] K. Scott, M. Eyre, D. McDuffee, A. E. Dorrance, *Plant Dis.* **2020**, *104*, 1421–1432.
- [2] a) H. Du, H. Peng, Faming Zhuanli Shenqing CN 111471237, 2020; b) L. Zheng, S. Zhang, Y. Xie, Z. Ding, X. Zhu, Faming Zhuanli Shenqing Gongkai Shuomingshu CN 101088986, 2007; c) A. S. Agnihotri, R. S. Deshpande, B. Shanker, Indian IN 182815, 1999; d) L. Nagy, J. Pelyva, P. Agocs, C. Soptei, Z. Kolonics, J. Benczik, S. Balini, D. Sebok, J. Cseke, PCT Int. Appl. WO 9320041, 1993.
- [3] B. Laroche, H. Ishitani, S. Kobayashi, Adv. Synth. Catal. 2018, 360, 4699–4704.
- [4] a) E. A. Artiukha, A. L. Nuzhdin, G. A. Bukhtiyarova, S. Y. Zaytsev, P. E. Plyusnin, Y. V. Shubin, V. I. Bukhtiyarov, *Catal. Sci. Technol.* 2015, *5*, 4741–4745; b) G. Chieffi, M. Braun, D. Esposito, *ChemSusChem* 2015, *8*, 3590–3594; c) C. Zor, H. A. Reeve, J. Quinson, L. A. Thompson, T. H. Lonsdale, F. Dillon, N. Grobert, K. A. Vincent, *Chem. Commun.* 2017, *53*, 9839–9841; d) H. W. Kim, S. Byun, S. M. Kim, H. J. Kim, C. Lei, D. Y. Kang, B. M. Kim, J. K. Park, *Catal. Sci. Technol.* 2020, *10*, 944–949.
- [5] a) B. Gutmann, D. Cantillo, C. O. Kappe, Angew. Chem. Int. Ed. 2015, 54, 6688–6728; Angew. Chem. 2015, 127, 6788–6832; b) R. Porta, M. Benaglia, A. Puglisi, Org. Process Res. Dev. 2016, 20, 2–25; c) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, Chem. Rev. 2017, 117, 11796–11893; d) F. M. Akwi, P. Watts, Chem. Commun. 2018, 54, 13894–13928; e) B. R. L. J. Bloemendal, M. A. C. H. Janssen, J. C. M. van Hest, F. P. J. T. Rutjes, React. Chem. Eng. 2020, 5, 1186–1197; f) F. Ferlin, D. Lanari, L. Vaccaro, Green Chem. 2020, 22, 5937–5955; g) A. I. Alfano, M. Brindisi, H. Lange, Green Chem. 2021, 23, 2233–2292; h) J. Jiao, W. Nie, T. Yu, F. Yang, Q. Zhang, F. Aihemaiti, T. Yang, X. Liu, J. Wang, P. Li, Chem. Eur. J. 2021, 27, 4817–4838.
- [6] a) N. G. Anderson, Org. Process Res. Dev. 2012, 16, 852–869; b) D. Dallinger, C. O. Kappe, Curr. Opin. Green Sustain. Chem. 2017, 7, 6–12; c) L. Rogers, K. F. Jensen, Green Chem. 2019, 21, 3481–3498.
- [7] Recent achievements in multistep continuous-flow research from other groups: a) S. B. Otvös, M. A. Pericas, C. O. Kappe, *Chem. Sci.* 2019, 10, 11141–11146; b) V.-E. H. Kassin, R. Gérardy, T. Toupy, D. Collin, E. Salvadeo, F. Toussain, K. Van Hecke, J.-C. M. Monbaliu, *Green Chem.* 2019, 21, 2839–3202; c) M. G. Russell, T. F. Jamison, *Angew. Chem. Int. Ed.* 2019, 58, 7678–7681; *Angew. Chem.* 2019, 131, 7760–7763; d) K. Hiebler, C. Dertnig, S. Soritz, M. C. Maier, T. R. Hörmann, B. Grabner, H. Gruber-Woelfler, *J. Flow Chem.* 2020, 10, 259–270; e) S. Chatterjee, M. Giudi, P. H. Seeberger, K. Gilmore, *Nature* 2020, 579, 379–384; f) S. B. Otvös, P. Llanes, M. A. Pericas, C. O. Kappe, *Org. Lett.* 2020, 22, 8122–8126.
- [8] a) S. Kobayashi, *Chem. Asian J.* 2016, *11*, 425–436;
 b) K. Masuda, T. Ichitsuka, N. Koumura, K. Sato, S.

Adv. Synth. Catal. 2021, 363, 1–7 Wiley Online Library 5 These are not the final page numbers!



Kobayashi, *Tetrahedron* 2018, 74, 1705–1730; c) H. Ishitani, Y. Saito, B. Laroche, X. Rao, S. Kobayashi, In *Flow Chemistry: Integrated Approaches for Practical Applications* Luis, S. V., Garcia-Verdugo, E. Eds., RSC Publishing, Cambridge, 2020, pp 1–49; d) W.-J. Yoo, H. Ishitani, Y. Saito, B. Laroche, S. Kobayashi, *J. Org. Chem.* 2020, 85, 5132–5145.

 [9] a) X. Hu, X. Hu, *Faming Zhuanli Shenqing CN* 111285770, 2020; b) X. Hu, X. Hu, *Faming Zhuanli* Shenqing CN 110551035, 2019; c) F. Fache, F. Valot, A. Milenkovic, M. Lemaire, *Tetrahedron* 1996, 52, 9777-9784.

[10] For example, when a 0.1 M toluene solution of 7 (0.1 mL/min), a 1.2 M DMF solution of 9 (0.01 mL/min), and a 0.25 MDMF solution of Tf₂NH (0.01 mL/min) were flowed into a 1/16 inch $\times 4$ m SUS coil reactor at 140 °C, the yield of 1 in the resulting solution was 44%. The residence time for this SUS coil reactor was estimated to be 16 min, however, the flow was relatively unstable and a long lead time was sometimes required.

COMMUNICATIONS

Two-Step Continuous-Flow Synthesis of Fungicide Metalaxyl through Catalytic C–N Bond-Formation Processes

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