Organic Syntheses

Copper and Secondary Amine-Catalyzed Pyridine Synthesis from *O*-Acetyl Oximes and α,β-Unsaturated Aldehydes

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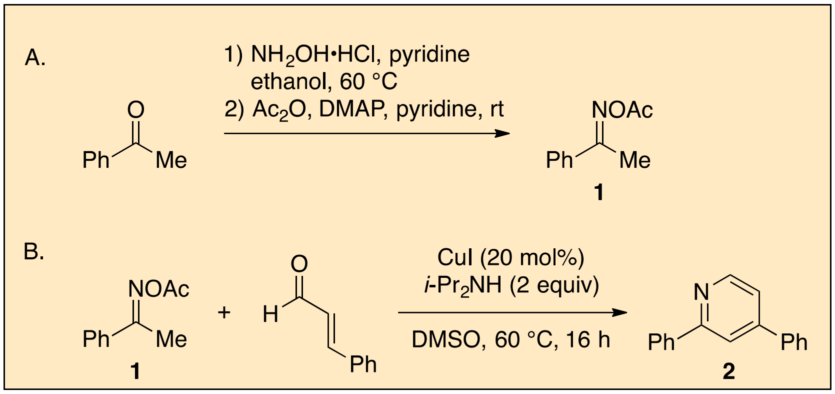

Procedure (Note 1)

A. *Acetophenone O-acetyl oxime* (**1**). A 250-mL, two-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (oval, 20 x 10 mm) is charged with acetophenone (9.33 mL, 80.0 mmol, 1 equiv) (Note 2), pyridine (18 mL, 223 mmol, 2.8 equiv) (Note 3), ethanol (40 mL) (Note 4), and hydroxylamine hydrochloride (8.33 g, 120 mmol, 1.5 equiv) (Note 5). The resulting mixture is stirred at 60 °C for 75 min (Notes 6 and 7) (Figure 1) and then cooled to 22 °C. Water (80 mL) is added, and the resulting biphasic mixture is transferred to a 500-mL separatory funnel. The mixture is partitioned, and the aqueous layer is extracted with ethyl acetate (2 x 80 mL). The organic extracts are combined, washed successively with 1 M HCl (50 mL) and brine (50 mL), and dried over anhydrous $MgSO_4$ (10 g) for 15 min. The extracts are gravity filtered through a filter paper and concentrated on a rotary evaporator (35 °C, 30 mmHg). The residue is transferred to a 250-mL, one-necked round-bottomed flask and dried further for 1 h under reduced pressure (1.5 mmHg, 22 °C) (Notes 8 and 9). A Teflon-coated stir bar (15 x 6 mm) is placed in the flask. To the flask are added *N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol, 0.002 equiv) (Note 10), pyridine (35 mL) (Note 2), and acetic anhydride (15 mL, 160 mmol, 2 equiv) (Note 11). The resulting mixture is stirred at room temperature (24 °C) for 1 h (Note 12). The volatile materials are removed on a rotary evaporator (45 °C, 35 mmHg). To the residue is added water (50 mL), and the mixture is transferred to a 250-mL separatory funnel. The mixture is partitioned, and the aqueous layer is extracted with ethyl acetate (2 x 50 mL). The organic extracts are combined, washed successively with 1 M HCl (50 mL) and brine (50 mL), and dried over anhydrous $MgSO_4$ (10 g) for 15 min. The extracts are filtered through a filter paper and concentrated on a rotary evaporator (35 °C, 30 mmHg). Recrystallization of the residual white

Figure 1. Reaction Setup for Step A (acetophenone oxime)

solid from ethyl acetate (Note 13) affords (*E*)-acetophenone *O*-acetyl oxime (**1**) as white crystals (9.41 g, 53.1 mmol, 66%) (Figure 2) (Notes 14, 15, and 16).

Figure 2. (*E*)-Acetophenone *O*-acetyl oxime (1)

B. *2,4-Diphenylpyridine* (**2**). An oven-dried, 500-mL, three-necked round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (oval, 30 x 16 mm) and the side neck is fitted with a glass gas inlet adapter connected to a vacuum/nitrogen manifold. The other side neck is capped with a glass stopper, and the center with a rubber septum (Figure 3). The flask is charged with **1** (6.19 g, 34.9 mmol) and copper(I) iodide (1.33 g, 6.98 mmol, 0.2 equiv) (Note 17). The flask is evacuated and backfilled with N_2 three times. To the flask are added cinnamaldehyde (6.6 mL, 52 mmol, 1.5 equiv) (Note 18), diisopropylamine (9.8 mL, 70 mmol, 2 equiv) (Note 19), and DMSO (175 mL) (Note 20) via syringe. The center neck is capped with a glass stopper, and the resulting mixture is stirred at 60 °C for 16 h under a gentle stream of nitrogen (Notes 21 and 22) (Figure 1). Upon cooling to room temperature, the reaction mixture is diluted with ethyl acetate (175 mL) and water (100 mL). The mixture is filtered through Celite (10 g) on a glass filter (Note 22) while washing with ethyl acetate (175 mL). The filtrate is transferred to a 1-L separatory funnel. The mixture is partitioned, and the organic layer is washed successively with water (150 mL) and brine

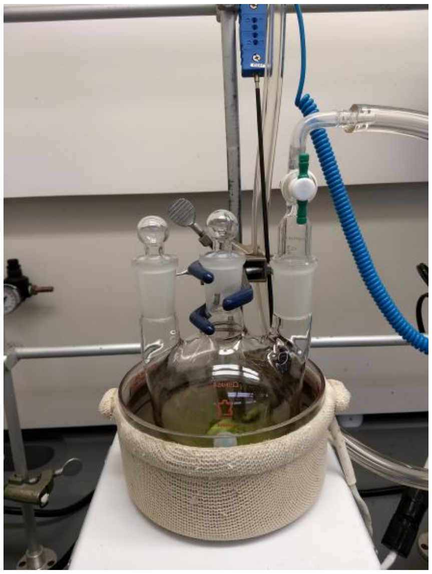

Figure 3. Reaction Setup for Step B

(50 mL), and dried over anhydrous $MgSO_4$ (15 g) for 30 min. The organic layer is filtered through Celite (10 g) on a glass filter (Note 23) and concentrated on a rotary evaporator (35 °C, 30 mmHg). The residue is transferred to a 25-mL flask and subjected to Kugelrohr distillation (Note 24) to remove excess cinnamaldehyde. The residue is subjected to column chromatography on silica gel (Note 25). The fractions containing the product are combined and concentrated on a rotary evaporator (35 °C, 30 mmHg), and the product is dried under reduced pressure at room temperature (1.5 mmHg, 2 h) to yield 2,4-diphenylpyridine (**2**) as a brown solid (5.17 g, 22.4 mmol, 64%) (Figure 4) (Notes 26, 27 and 28).

Figure 4. 2,4-Diphenylpyridine (2)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with acetophenone, pyridine, ethanol, hydroxylamine hydrochloride, ethyl acetate, hydrochloric acid, magnesium sulfate, *N*,*N*-dimethylaminopyridine, acetic anhydride, copper(I) iodide, cinnamaldehyde, diisopropylamine, dimethylsulfoxide, and Celite, as well as the proper procedures for operation of a Kugelrohr apparatus.
2. Acetophenone (99%) was purchased from Alfa Aesar and used as received.
3. Anhydrous pyridine (99.8%) was purchased from Sigma-Aldrich and used as received.
4. Anhydrous, denatured ethanol was purchased from Sigma-Aldrich and used as received.
5. Hydroxylamine hydrochloride (99%) was purchased from Alfa Aesar and used as received.
6. A 1.2-L oil bath was used, and stirring was performed at 450 rpm. After 5 min of heating, the white solids of hydroxylamine hydrochloride were completely dissolved and a colorless solution was obtained. No color change was observed over the course of the reaction.
7. The reaction progress was monitored by TLC analysis on Merck silica gel 60 F_{254} plates with hexane/ethyl acetate (9:1) as the eluent. The TLC

plates were visualized under 254 nm UV lamp. The R_f values of acetophenone and acetophenone oxime are 0.31 and 0.20, respectively.

8. A Schlenk line equipped with an oil pump was used. A colorless solid (ca. 12 g) containing some residual solvents, which did not interfere with the next step, was obtained.
9. The characterization data of the non-purified acetophenone oxime are as follows: ATR-FTIR: 3236, 1497, 1370, 1302, 1005, 925 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 7.41-7.43 (m, 3H), 7.65-7.66 (m, 2H), 9.79 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.5, 126.2, 128.7, 129.4, 136.6, 156.1; HRMS (ESI) *m/z* calcd for $C_8H_{10}NO$ $[M+H]^+$ 136.0762, found 136.0765.
10. 4-(Dimethylamino)pyridine (99%) was purchased from Alfa Aesar and used as received.
11. Acetic anhydride (99+%) was purchased from Acros and used as received (checkers). Acetic anhydride (98%) was purchased from Merck KGaA and used as received (submitters).
12. The reaction progress was monitored by TLC analysis on Merck silica gel 60 F_{254} plates with hexane/*tert*-butyl methyl ether (4:1) as the eluent. The TLC plates were visualized under 254 nm UV lamp. Acetophenone oxime and **1** show the R_f value of 0.35 and 0.2, respectively.
13. Recrystallization was performed as follows: Ethyl acetate (5 mL) was added to the crude residue and the flask equipped with a condensor. The mixture was gently heated until all the solids were dissolved. The solution was left to cool to room temperature and then placed in an ice bath to grow white crystalline solids. The solids were collected by filtration through a Büchner funnel and washed with ice-cold hexane (100 mL).
14. Acetophenone *O*-acetyl oxime (**1**) has the following physical properties: mp = 56–57 °C; ATR-FTIR: 1758, 1615, 1571, 1445, 1361, 1308, 1203, 1002, 978, 934, 892 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 2.38 (s, 3H), 7.38-7.45 (m, 3H), 7.73-7.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 19.9, 127.1, 128.7, 130.7, 135.0, 162.5, 169.0; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}NO_2$ $[M+H]^+$ 178.0868, found 178.0866. The compound was evaluated by DSC (Differential Scanning Calorimetry), which indicates the compound should never be heated above ~150 °C.
15. The purity was determined to be >99% wt. by quantitative ^{1}H NMR spectroscopy in $CDCl_3$ using 31.5 mg of the compound **1** and 16.1 mg of dimethyl fumarate as an internal standard.

16. A second reaction on the same scale provided 9.88 g (70%) of the product.
17. CuI (98%) was purchased from Strem Chemicals and used as received.
18. *trans*-Cinnamaldehyde (98%) was purchased from Alfa Aesar and purified by Kugelrohr distillation (120 °C, 2.3 mmHg).
19. Diisopropylamine (99.5%) was purchased from Aldrich and purified by distillation over CaH_2 (checkers). Diisopropylamine (99+%) was purchased from Alfa Aesar and purified by distillation over CaH_2 (submitters).
20. Anhydrous DMSO was purchased from Alfa Aesar and used as received.
21. A 1.2-L oil bath was used, and stirring was performed at 450 rpm. During the initial 15 min of heating, the reaction turned from light green to dark green to black.
22. The reaction progress was monitored by TLC analysis on Merck silica gel 60 F_{254} plates with hexane/ethyl acetate (9:1) as the eluent. The TLC plates were visualized under 254 nm UV lamp and then with 2,4-dinitrophenylhydrazine stain. R_f values of **1**, **2**, and cinnamaldehyde are 0.20, 0.32 and 0.32 respectively. Only cinnamaldehyde turns red/orange immediately after dipping into 2,4-dinitrophenylhydrazine stain.
23. The specifications of the glass filter are as follows: Volume 150 mL, OD 60 mm, porosity 40-60 μm.
24. Kugelrohr distillation was performed at 120 °C under 0.75 mmHg for 90 min.
25. The crude material is dissolved in dichloromethane (4 mL) and then charged onto a column (diameter = 7 cm, height (silica height) = 11 cm) of 190-gram silica gel. The column is first eluted with hexane (100 mL), then (sequentially) eluted with hexane/ethyl acetate = 95:5 (500 mL), hexane/ethyl acetate = 92:8 (1000 mL), hexane/ethyl acetate = 90:10 (500 mL), hexane/ethyl acetate = 88:12 (500 mL). The first 500 mL eluent was not collected, and then 13-14-mL fractions were collected. Fractions 71-108 were combined and concentrated on a rotary evaporator (35 °C, 30 mmHg).
26. 2,4-Diphenylpyridine (**2**) has the following physical properties: mp = 66–67 °C; ATR-FTIR: 1604, 1592, 1577, 1540, 1493, 1468, 1447, 1388, 1074, 988, 885, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43-7.53 (m, 7H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.93 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 8.75 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 118.9, 120.4, 127.16, 127.2, 128.9,

129.14, 129.15, 129.2, 138.7, 139.6, 149.4, 150.2, 158.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N$ $[M+H]^+$ 232.1126, found 232.1120.

27. The purity was determined to be >99% wt. by quantitative ^1H NMR spectroscopy in $CDCl_3$ using 23.5 mg of the compound **2** and 12.4 mg of dimethyl fumarate as an internal standard.
28. A second reaction on the same scale provided 5.41 g (67%) of the product.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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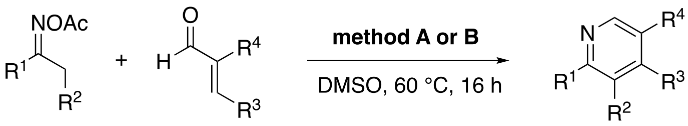
Discussion

The efficient and regioselective synthesis of substituted pyridines represents one of the most important subjects in heterocyclic chemistry, and is relevant to medicinal and materials chemistry because of the prevalence of the pyridine core in pharmaceuticals and other organic functional materials. Besides conventional methods based on carbonyl condensation chemistry, a variety of alternative approaches, those catalyzed by transition metals in particular, have been extensively explored to date.[2] In this context, oxime derivatives have emerged as readily available and versatile starting materials for the synthesis of pyridines and other nitrogen-containing heterocycles under transition metal catalysis.[3] For example, Liebeskind developed [4+2]-type pyridine synthesis via copper-catalyzed C–N coupling between alkenylboronic acid and α,β-unsaturated oxime *O*-pentafluorobenzoate and subsequent electrocyclization.[4] α,β-Unsaturated oxime derivatives have also been exploited for [4+2]-type pyridine synthesis via rhodium-catalyzed, oxime-directed C–H activation and annulation with alkynes[5] or alkenes.[6]

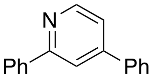
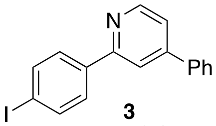
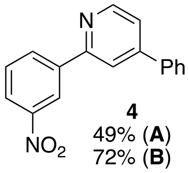
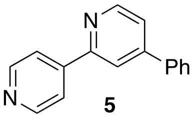
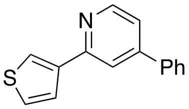
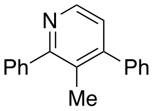
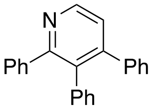
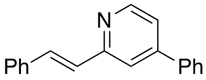
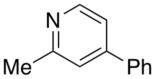
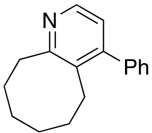
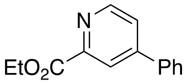
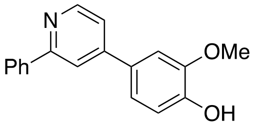
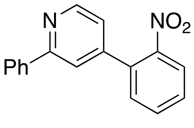
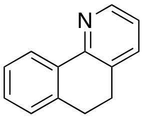
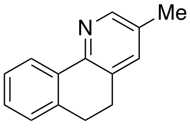
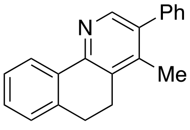
The pyridine synthesis described here is based on our previous work on the [3+3]-type condensation of oxime acetates having α-protons with α,β-unsaturated aldehydes in the presence of a copper(I) salt and a secondary amine (or ammonium salt).[7] We developed two viable catalytic systems for this transformation. One comprises catalytic amounts (20 mol% each) of CuI and pyrrolidinium perchlorate (denoted as method A), while the other employs catalytic CuI (20 mol%) in combination with a superstoichiometric amount (2 equiv) of diisopropylamine (denoted as method B). As briefly summarized in Table 1, both methods A and B are effective for the condensation of oximes derived from acetophenone and related aryl ketones with cinnamaldehyde derivatives (see the products **2**–**8**). On the other hand, only method B is practicable for oximes derived from other types of ketones (see the products **9**–**12**). In addition, there remains room for improvement for the reaction of unsaturated aldehydes other than cinnamaldehyde derivatives (see the products **15**–**17**).

In this report, the synthesis of 2,4-diphenylpyridine on a multigram scale is described in detail. Here, method B was chosen because diisopropylamine would be in the list of commodity chemicals of most synthetic laboratories. While the synthesis of 2,4-diphenylpyridine itself was achieved in many different ways (e.g., cross-coupling between 2,4-

Table 1. Selected pyridines obtained by the copper/amine-catalyzed condensation (previous work)[a]



method A: CuI (20 mol%), pyrrolidinium perchlorate (20 mol%)
method B: CuI (20 mol%), *i*-Pr_2NH (2 equiv)

 **2** 75% (**A**)[b] 84% (**B**)[b]	 **3** 78% (**A**) 66% (**B**)	 **4** 49% (**A**) 72% (**B**)	 **5** 42% (**A**) 79% (**B**)
 **6** 85% (**A**) 78% (**B**)	 **7** 80% (**A**) 92% (**B**)	 **8** 80% (**A**) 92% (**B**)	 **9** 20% (**A**)[c] 55% (**B**)
 **10** <10% (**A**)[c] 65% (**B**)	 **11** <10% (**A**)[c] 79% (**B**)	 **12** <10% (**A**)[c] 52% (**B**)	 **13** 75% (**A**) 76% (**B**)
 **14** 79% (**A**)[d] 80% (**B**)	 **15** 36% (**B**)[e]	 **16** 23% (**A**)[f] 72% (**B**)[f]	 **17** 36% (**A**)[g]

[a] Unless otherwise noted, the reaction was performed using 0.2 mmol of oxime acetate and 0.3 mmol (1.5 equiv) of α,β-unsaturated aldehyde. [b] 10 mmol-scale reaction. [c] Determined by GC. [d] 40 mol% of CuI was used. [e] 5 equiv of acrolein was used. [f] 2 equiv of methacrolein was used. [g] 3 equiv of aldehyde was used.

dihalopyridine and phenylmetal reagents), there had been practically no general method for the synthesis of diversely substituted 2,4-diarylpyridines from simple starting materials. Indeed, many of the pyridine products described in our previous work[7] had not been reported before.

From a mechanistic point of view, the present condensation reaction capitalizes on the ability of copper(I) to reduce the oxime N–O bond[8] as well as that of secondary amine (or ammonium) to activate an aldehyde via iminium formation. Thus, the copper catalyst would reduce the oxime acetate via sequential single-electron transfer to generate an iminylcopper(II), which would then tautomerize to a nucleophilic copper(II) enamide species.[9] A Michael addition of the copper enamide to the α,β-unsaturated iminium and subsequent cyclocondensation would give a dihydropyridine intermediate while liberating the secondary amine. The dihydropyridine would be oxidized by copper(II) to furnish the pyridine and regenerate copper(I). The overall reaction mechanism may be understood in terms of synergistic catalysis of copper(I) and amine.[10]

Since our report, a few variants of the present reaction have been reported. Cui et al. developed a copper-catalyzed three-component condensation of an oxime pivalate, an aldehyde, and malononitrile to afford a 2-aminonicotinonitrile derivative,[11] while Jiang et al. developed an analogous three-component condensation of an oxime acetate, an aldehyde, and a β-keto ester to afford a multi-substituted pyridine.[12] These reactions most likely involve the formation of an activated Michael acceptor via Knoevenagel condensation. Huang, Deng, and coworkers reported a metal-free system employing iodine and triethylamine, as an alternative to the present copper/amine system, for the condensation of an oxime acetate and an α,β-unsaturated aldehyde.[13] Despite the simplicity, the system requires a higher reaction temperature (120 °C) and appears to have a narrower scope than that of the present method, as it is not applicable to oximes derived from dialkylketones. Besides these reports, several other transition metal-catalyzed pyridine-forming reactions employing oxime acetates bearing α-protons have been reported.[14]

In conclusion, the copper/amine-catalyzed method developed by us allows for convenient preparation of certain types of substituted pyridines, some of which may not be readily accessible by conventional methods. The method shows excellent functional group compatibility and tolerates scale-up.

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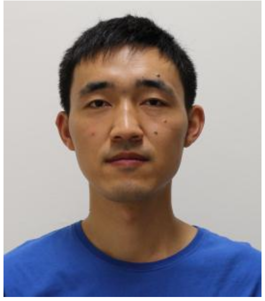
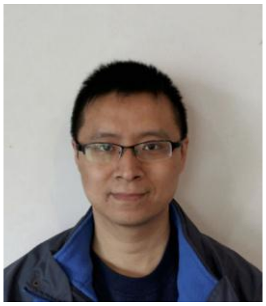
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Acetophenone: Ethanone, 1-phenyl-; (98-86-2)
Hydroxylamine hydrochloride: Hydroxylamine, hydrochloride (1:1); (5470-11-1)
Pyridine: Pyridine; (110-86-1)
N,*N*-Dimethylaminopyridine: 4-Pyridinamine, *N*,*N*-dimethyl-; (1122-58-3)
Acetic anhydride: Acetic acid, 1,1'-anhydride; (108-24-7)
Copper(I) iodide: Copper iodide; (7681-65-4)
Diisopropylamine: 2-Propanamine, *N*-(1-methylethyl)-; (108-18-9)
trans-Cinnamaldehyde: 2-Propenal, 3-phenyl-, (2*E*)-; (14371-10-9)

Wei Wen (Simon) Tan was born in Singapore. He received his B.Sc. (1st class honors) degree in chemistry and biological chemistry from Nanyang Technological University in 2013. He ~~expects to~~ received his Ph.D. degree in chemistry from Nanyang Technological University in 2017 under the supervision of Professor Naohiko Yoshikai, working on the ~~. His research was focused on~~ the development of novel copper-catalyzed condensation methods for the synthesis of heteroarenes. He then joined Mondelēz International as a flavour scientist.

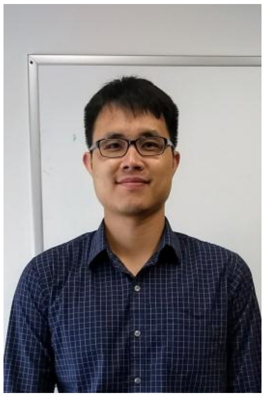


Bin Wu received his B.Sc. degree in 2009 and M.Sc. degree in 2012 (both in chemistry) from Soochow University. He subsequently moved to Singapore and ~~enrolled as~~obtained ~~a~~ his Ph.D. ~~student~~ degree ~~in~~ under the guidance of Prof. Naohiko Yoshikai~~'s group at~~ from Nanyang Technological University in 2017. ~~His research is focused on the development of novel synthetic approaches to heteroatom-bridged π-conjugated systems. He has defended his doctoral thesis in January 2017 and is currently working as a research associate~~After a brief stint as a postdoctoral associate in the same group, ~~.~~he joined Novartis Pharma in Suzhou (China) as a Senior Scientist. His current research focuses on the process research and development of drug substances.



Ye Wei was born in 1982 in China. He earned his B.Sc. degree in 2005 from Huaqiao University and his Ph.D. degree in 2010 from Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, under the guidance of Prof. Weiping Su. After a two-year postdoctoral appointment with Prof. Naohiko Yoshikai at Nanyang Technological University, he went back to China to join the College of Pharmacy at Third Military University. He was promoted to Professor in 2015. His research interests are primarily focused on transition metal-mediated novel organic transformations to construct heterocyclic scaffolds.

Naohiko Yoshikai was born in 1978 and raised in Tokyo. He received his B.Sc. (2000), M.Sc. (2002), and Ph.D. (2005) degrees from the University of Tokyo under the guidance of Professor Eiichi Nakamura. He then served as an Assistant Professor at the same institute (2005-2009). In 2009, he moved to Singapore to join the faculty of Nanyang Technological University as an Assistant Professor and a Research Fellow of the Singapore National Research Foundation. He has been an Associate Professor since 2016. His research interests revolve around the development and mechanistic study of novel transition metal-catalyzed reactions and their synthetic applications.



Suttipol Radomkit was born in 1986 in Thailand. He received his B.S. (2008) in Chemistry from Kasetsart University and M.S. (2010) in Chemical Biology from Chulabhorn Graduate Institute, Thailand. He obtained his Ph.D. under the guidance of Professor Amir H. Hoveyda from Boston College in 2016. He then joined Boehringer Ingelheim Pharmaceuticals Inc. in Ridgefield, CT where he is currently a Senior Scientist. His research focuses on the design and development of practical synthetic methods for drug candidates.