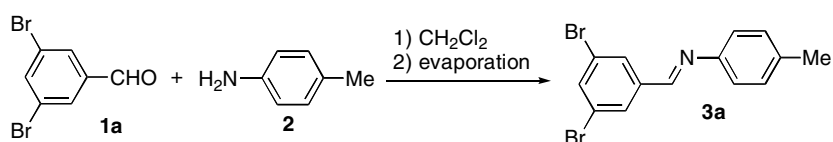


Rate Acceleration of Organic Reaction by Immediate Solvent Evaporation

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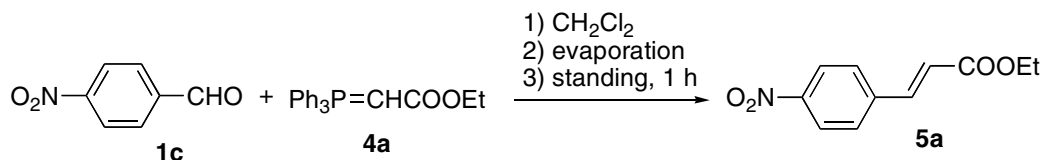
Representative ISEM procedure for imine (Table 1, Entry 1): In a round-bottom flask were placed **1a** (527.9 mg, 2.0 mmol) and **2** (235.7 mg, 2.2 mmol), and CH₂Cl₂ (4 mL) was added. The clear solution was evaporated in vacuo at 27 °C for 5 min, and, during evaporation, transparent film was formed. Analysis of the film by ¹H NMR showed consumption of **1a**.

3a: ¹H NMR (CDCl₃) 500 MHz: δ 2.38 (s, 3H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.75 (s, 1H), 7.98 (s, 2H), 8.35 (s, 1H).

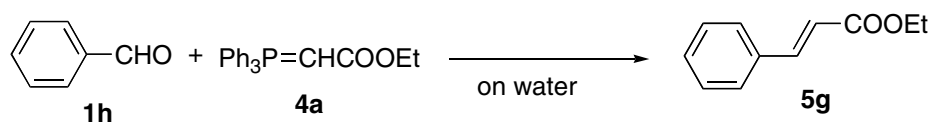
3b: ¹H NMR (CDCl₃) 500 MHz: δ 2.38 (s, 3H), 7.14 (d, *J* = 14 Hz, 2H), 7.21 (d, *J* = 14 Hz, 2H), 7.44 (t, *J* = 3.1 Hz, 1H), 7.78 (d, *J* = 3.1 Hz, 2H), 8.37 (s, 1H).

3c: ¹H NMR (CDCl₃) 500 MHz: δ 2.38 (s, 3H), 7.21 (q, *J* = 11.0 Hz, 4H), 8.5 (d, *J* = 8.6 Hz, 2H), 8.31 (d, *J* = 8.6 Hz, 2H), 8.71 (s, 1H).

3d: ¹H NMR (CDCl₃) 500 MHz: δ 2.38 (s, 3H), 7.21 (q, *J* = 5.5 Hz, 4H), 7.56–7.51 (m, 2H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.91 (t, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 8.18 (s, 1H), 8.62 (s, 1H).



Representative ISEM procedure for Wittig reaction (Table 2, Entry 1): In a round-bottom flask were placed **1c** (302.2 mg, 2.0 mmol) and **4a** (766.4 mg, 2.2 mmol), and CH₂Cl₂ (4 mL) was added. The clear solution was evaporated at 27 °C for 5 min, and, during evaporation, a solid film was formed. After the film had been kept in vacuo at rt for 1 h, a portion of the film was dissolved in CDCl₃. Analysis of the film by ¹H NMR showed complete consumption of **1c**. The crude products were subjected to a column chromatography on silica gel (30% AcOEt/hexane) to give **5a** in a pure form (93% yield). **5a**: ¹H NMR (CDCl₃) 500 MHz: (*E* : *Z* = 99 : 1) δ 1.36 1.25 (t, 7.1 Hz, 3H), 4.30 4.17 (q, *J* = 7.1 Hz, 2H), 6.55 6.13 (d, *J* = 16.1 12.6 Hz, 1H), 7.71 7.02 (d, *J* = 16.1 12.6 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 2H), 8.25 (d, *J* = 8.9 Hz, 2H).



Sharpless procedure for Wittig reaction: To a round-bottom flask were added **4a** (766.4 mg, 2.2 mmol) and water (10 mL). To this suspension was added **1h** (212.2 mg, 2.0 mmol), and the mixture was stirred at 27 °C for 1.5 h. While the mixture was stirred, white precipitate appeared. After hexane (10 mL) had been added, the organic phase was separated. Analysis by ¹H NMR showed consumption of **1h**. Evaporation gave **5g** in a pure form. **5g**: ¹H NMR (CDCl₃) 500 MHz: (*E* : *Z* = 94 : 6) δ 1.34 1.24 (t, 7.4 Hz, 3H), 4.27 4.17 (q, *J* = 7.4 Hz, 2H), 6.43 5.95 (d, *J* = 15.9 12.6 Hz, 1H), 7.69 6.95 (d, *J* = 15.9 12.6 Hz, 1H), 7.34-7.39 (m, 2H), 7.52-7.59 (m, 2H).

5a,c g and h: Ying Chen, Lingyu Huang, Meera A. Ranade, and X. Peter Zhang,

J. Org. Chem., **2003**, *68*, 3714-3717.

5b: Zhu, Yulin; Pan, Yuanjiang. *Chem. Lett.* **2004**, *33*, 668-669.

5d: Albrecht, Markus; Riether, Cyrill. *Synthesis*, **1997**, 957-962.

5e: Arjunan, Palanisamy; Shymasundar, Nagaraj; Berlin, K. Darrell; Najjar, Dada; Rockley, Mark G. *J. Org. Chem.* **1981**, *46*, 626-9.

5f: Kisanga, P.; D'Sa, B.; Verkade, J. *Tetrahedron*, **2001**, *57*, 8047-8052.

Representative ISEM procedure for phosphonium salts 8a (Table 3, ISEM): In a round-bottom flask were placed **7a** (442.0 mg, 2.0 mmol) and **6** (576.8 mg, 2.2 mmol), and acetone (4 mL) was added. The clear solution was evaporated at 27 °C for 5 min, and, during evaporation, a solid film was formed. A portion of the film was dissolved in CDCl₃. ¹H NMR showed the film was composed of a 91:9 mixture of **8a** and **7a**. After the film had been kept in vacuo at rt for 2 h, a portion of the film was dissolved in CDCl₃. Analysis of the film by ¹H NMR showed complete consumption of **7a**. The crude products were washed with acetone to furnish **8a** in a pure form (91% yield). **8a**: ¹H NMR (CDCl₃) 500 MHz: δ 5.63 (d, *J* = 14.0 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.40-7.46 (m, 2H), 7.55-7.64 (m, 9H), 7.72-7.80 (m, 2H).

Lee, K. Y.; Na, J. E.; Lee, M. J.; Kim, N. *Tetrahedron Lett.* **2004**, *45*, 5977.

8b: ¹H NMR (CDCl₃) 300 MHz: δ 5.70 (d, *J* = 15.1 Hz, 2H), 7.31 (q, 2H), 7.45 (t, 2H), 7.55 (d, *J* = 10.0 Hz, 3H), 7.60-7.70 (m, 6H), 7.70-7.83 (m, 11H).

Preparation of 9: An acetonitrile solution (20 mL) of 4,4'-bipyridine (642.7 mg, 4.0 mmol) and 4-bromobenzyl bromide (249.9 mg, 1.0 mmol) was heated at 60 °C for 2

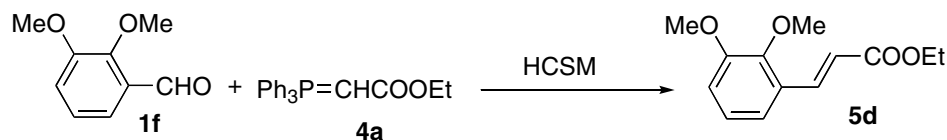
h. The mixture was filtered, and the filtrate was evaporated. The residual solids were washed with Et₂O. The solid was dissolved in a mixture of acetone (30 mL) and water (15 mL), and NH₄PF₆ (1.63 g, 10.0 mmol) was added. After evaporation, water (100 mL) was added. While the solution was kept at rt for 2 h, white precipitate appeared. The solid was filtered and washed with water (5 mL) and Et₂O (5 mL) to furnish **9** in a pure form (80 % yield).

9: ¹H NMR (CD₃COCD₃) 300 MHz: δ 9.35 (d, J = 6.9 Hz, 4H), 8.86 (m, 2H), 8.68 (d, J = 6.9 Hz, 2H), 7.98 (d, J = 6.0 Hz, 4H), 7.71-7.63 (q, 4H), 6.11 (s, 2H); ¹³C NMR (CD₃COCD₃) 75 MHz: δ 155.5, 152.1, 146.4, 142.0, 133.7, 133.4, 132.2, 127.2, 124.5, 122.7, 64.3.

ISEM procedure for pyridinium salt 10 (Table 4): In a round-bottom flask were placed **7a** (486.2 mg, 2.2 mmol) and **9** (492.2 mg, 2.0 mmol), and acetone (4 mL) was added. The clear solution was evaporated at 27 °C for 5 min, and, during evaporation, a solid film was formed. A portion of the film was dissolved in DMSO-*d*₆. ¹H NMR showed the film was composed of a 80:20 mixture of **10** and **9**. After the film had been kept in vacuo at rt for 3 h, a portion of the film was dissolved in DMSO-*d*₆. Analysis of the film by ¹H NMR showed complete transformation of **9** to **10**. For purification of the product, bromide **10** was transformed to PF₆ salt **10'**. To the film were added NH₄PF₆ (3.26 g, 20 mmol), acetone (330 mL), CHCl₃ (130 mL) and water (67 mL) and the mixture was shaken vigorously. The organic phase was separated and evaporated. The residue was subjected to column chromatography on silica gel (MeOH : CH₂Cl₂ : MeNO₂ : 2M NH₄Cl aq = 70 : 16 : 11 : 3) to furnish **10'** in a pure form (73% yield).

10': ¹H NMR (CD₃COCD₃) 300 MHz: δ 9.60 (d, J = 6.9 Hz, 2H), 9.53 (d, J = 6.9 Hz, 2H), 8.85 (d, J = 6.9 Hz, 4H), 8.25 (s, 1H), 8.05-7.94 (m, 3H), 7.73-7.60 (m, 7H), 6.36 (s, 2H), 6.18 (s, 2H).

¹³C NMR (CD₃COCD₃) 75 MHz: δ 155.4, 146.9, 134.2, 133.5, 133.4, 132.3, 131.4, 130.5, 130.4, 129.2, 128.7, 128.7, 128.6, 128.5, 128.3, 127.9, 126.7, 124.6, 65.9, 64.9.



Effect of concentration of HCSM procedure for Wittig reaction in 0.4-2.0 mL of CH₂Cl₂ (Representative procedure in 2 mL): CH₂Cl₂ required for a reaction (column A) was to be divided to 2 portions: 1.6 mL for **1f** (column B) and 0.4 mL for **4a** (column D). Aldehyde **1f** (1.0 mmol) and 1.60 mL of CH₂Cl₂ were added to a 2 mL measuring flask, and then CH₂Cl₂ was added by a syringe until the solution reached 2.0 mL. Because an amount of the solution became 2.0 mL when 0.25 mL was added, the total volume of CH₂Cl₂ (1.6 mL) and **1f** (1.0 mmol) was found to be 1.75 mL (column C). Similarly, the total volume of the CH₂Cl₂ (0.4 mL) and ylide **4a** (1.1 mmol) was found to be 0.75 mL (column E).

For 1 mmol-scale reaction, the CH₂Cl₂ solutions of **1f** and **4a** were prepared in 2 mmol scale, and the required amounts of the solutions were used as follows. A CH₂Cl₂ solution of **1f** was prepared from 3.2 mL of CH₂Cl₂ and 332.4 mg (2.0 mmol), and another CH₂Cl₂ solution was prepared from 0.80 mL of CH₂Cl₂ and 766.4 mg (2.2 mmol) of **4a**. To a round-bottom flask were added CH₂Cl₂ solution of **1f** (1.75 mL, corresponding to 166.2 mg [1.0 mmol] of **1f** in 1.60 mL of CH₂Cl₂) and CH₂Cl₂ solution of **4a** (0.75 mL, corresponding to 383.2 mg [1.1 mmol] of **4a** in 0.40 mL of CH₂Cl₂). This mixture was kept at rt for 5 min, and 5 mL of CH₂Cl₂ was added at 0 °C. A few drops of this solution was added to CDCl₃, and a ratio of the enone and the aldehyde was determined by ¹H NMR (35.6 : 64.4).

| A | B | C | D | E | F |
|---|--|--|---|---|----------------------------|
| Sum of CH ₂ Cl ₂ for Wittig reaction (mL) | CH ₂ Cl ₂ (mL) to dissolve aldehyde (1 mmol) | Amount of CH ₂ Cl ₂ solution (mL) of aldehyde (1 mmol) | CH ₂ Cl ₂ (mL) to dissolve ylide (mmol) | Amount of CH ₂ Cl ₂ solution (mL) of ylide (mmol) | Ratio (product : aldehyde) |
| 2.00 | 1.60 | 1.75 | 0.40 | 0.75 | 35.6 : 64.4 |
| 1.00 | 0.60 | 0.75 | 0.40 | 0.75 | 43.9 : 56.1 |
| 0.80 | 0.40 | 0.55 | 0.40 | 0.75 | 46.4 : 53.6 |
| 0.70 | 0.30 | 0.45 | 0.40 | 0.75 | 48.9 : 51.1 |
| 0.60 | 0.20 | 0.35 | 0.40 | 0.75 | 52.1 : 47.9 |

| | | | | | |
|------|------|------|------|-------|-------------|
| 0.55 | 0.15 | 0.30 | 0.40 | 0.75 | 53.9 : 46.1 |
| 0.50 | 0.10 | 0.25 | 0.40 | 0.75 | 55.8 : 44.2 |
| 0.45 | 0.05 | 0.20 | 0.40 | 0.75 | 57.9 : 42.1 |
| 0.40 | 0.05 | 0.20 | 0.35 | 0.675 | 59.5 : 40.5 |

Effect of concentration of HCSM procedure for Wittig reaction in 0.1-0.35 mL of CH₂Cl₂: In a round-bottom flask were placed 166.2 mg (1.0 mmol) of **1f** and 383.2 mg (1.1 mmol) of **4a**. To the mixture was added 0.35 mL of CH₂Cl₂, and the suspension was stirred at 27 °C for 5 min. After 5 mL of CH₂Cl₂ had been added at 0 °C, a few drops of this solution was added to CDCl₃, and a ratio of the enone and the aldehyde was determined by ¹H NMR (57.5 : 42.5).

| | CH ₂ Cl ₂ (mL) | Ratio (product : aldehyde) |
|---|--------------------------------------|----------------------------|
| 1 | 0.35 | 57.5 : 42.5 |
| 2 | 0.30 | 54.7 : 45.3 |
| 3 | 0.20 | 49.4 : 50.6 |
| 4 | 0.10 | 42.7 : 57.3 |

