Fluorous tagging: an enabling isolation technique for indium-mediated allylation reactions in water†

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An efficient method was developed to allylate aldehydes using an aqueous indium-mediated allylation reaction with fluorous-tagged allyl halides, and to directly purify the products by fluorous solid phase extraction (F-SPE).

The fluorous technologies recently established by Horváth,[1] Gladysz,[2] and Curran[3] provide innovative methods for biphasic catalysis, catalyst recycling, and reaction product purification. In particular, the concept of fluorous tagging, the attachment of fluorous fragments to organic substrates, allows simple separation of organic compounds based on their fluorine content.[4]

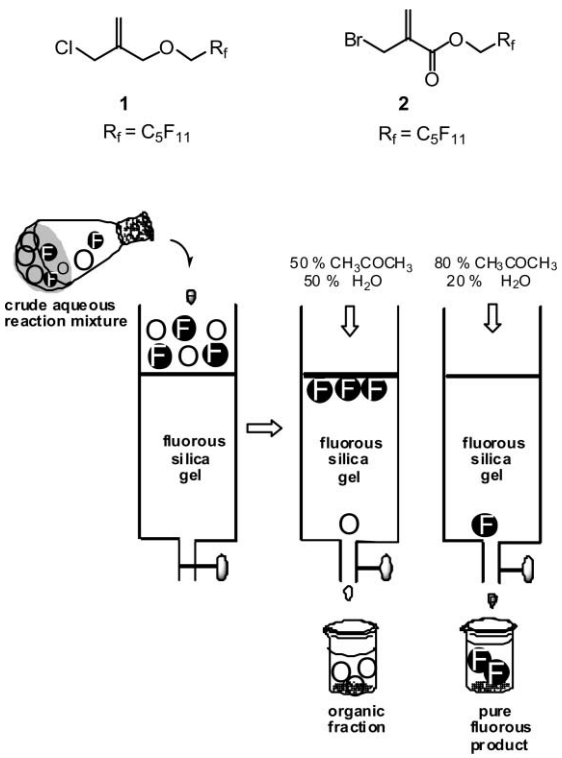
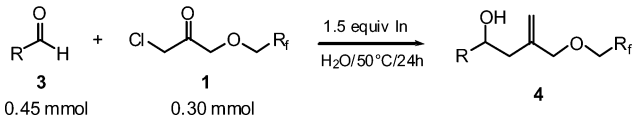
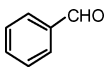
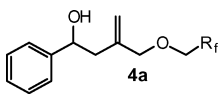
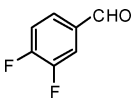
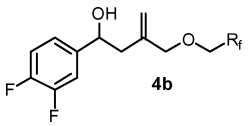
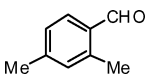
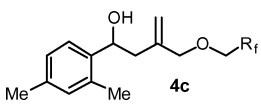
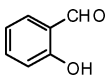
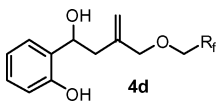
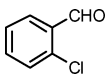
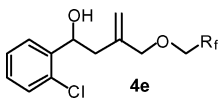
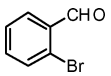
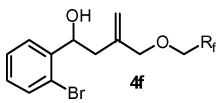
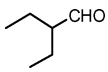
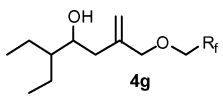
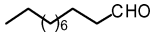
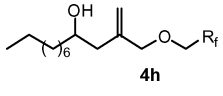


Fig. 1 Fluorous-tag technique for product isolation in aqueous reactions.

Indium-mediated Barbier–Grignard-type allylation of aldehydes in water[5] provides various synthetic advantages including: (1) the elimination of the need for inert atmosphere and anhydrous organic solvent; (2) allowing direct use of compounds bearing highly reactive functional groups without the need for protection and deprotection steps; and (3) the direct use of water-soluble starting materials without pre-derivatizations. The reaction has led to the efficient synthesis of various natural products.[6]

Table 1 Allylation of aldehydes with fluorinated allyl ethers



Entry	Aldehyde	Product **4**	Yield (%)[a]
1		 **4a**	98
2		 **4b**	44
3		 **4c**	87
4		 **4d**	66
5		 **4e**	81
6		 **4f**	92
7		 **4g**	78
8		 **4h**	39

[a] Isolated yield after F-SPE using water as solvent.

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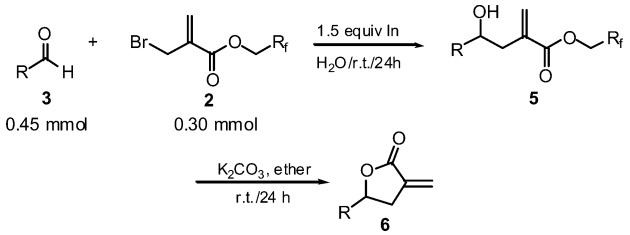
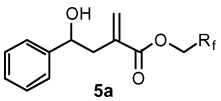
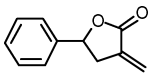
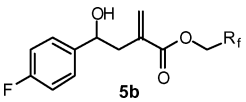
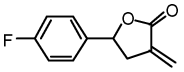
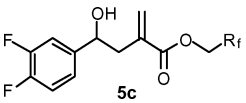
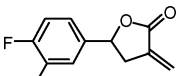
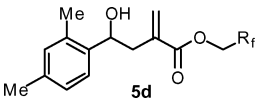
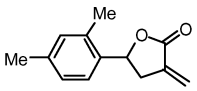
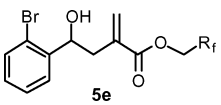
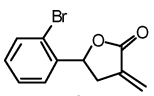
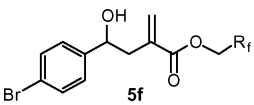
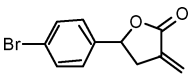
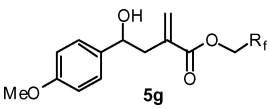
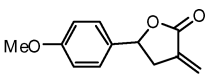
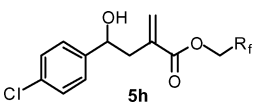
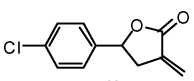
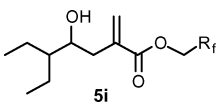
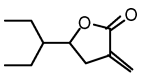
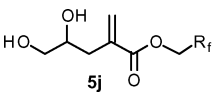
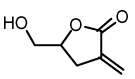
However, there are still some limitations of the reaction at the current stage: (1) product isolation by extraction with organic solvent consumes a large amount of organic solvent as well as leaving a significant amount of solvent residue in aqueous solution; and (2) for water-soluble products, water has to be evaporated completely (often by freeze-drying) before further purification, which is both time-consuming and energy-intensive. Similar limitations exist in other aqueous reaction systems. Thus, an innovative method to isolate the products of such aqueous reactions efficiently avoiding extraction and/or freeze-drying

Table 2 Synthesis of α-methylene-γ-butyrolactones by allylation of aldehydes with fluorinated allyl ester **2**



Entry	Product **5**	Yield (%)	Product **6**	Yield (%)[a]
1	 **5a**	86	 **6a**	88
2	 **5b**	80	 **6b**	83
3	 **5c**	76	 **6c**	84
4	 **5d**	85	 **6d**	Trace
5	 **5e**	74	 **6e**	Trace
6	 **5f**	54	 **6f**	91
7	 **5g**	90	 **6g**	73
8	 **5h**	72	 **6h**	98
9	 **5i**	49	 **6i**	89
10	 **5j**	20[b]	 **6j**	80

[a] Isolated yield after F-SPE using water as solvent. [b] Acetone–water (1 : 1) as solvent.

techniques is highly desirable. Herein, we wish to report the use of a shorter fluorous tag in synthesis and purification in aqueous reaction systems. By using the fluorous-tag chemistry, an isolation technique was developed for indium-mediated allylation reactions in water. The corresponding products were isolated readily by simple filtration through a short plug of fluorous silica gel (Fig. 1).

To begin our study, two different types of fluorous-tagged allylating reagents **1** and **2** were synthesized.[7] With these allylating reagents in hand, their reactions with various aldehydes were then examined. We reacted compound **1** (117 mg, 0.30 mmol) with benzaldehyde (48 mg, 0.45 mmol) and In powder (52 mg, 0.45 mmol) in 4 mL water at 50 °C in air for 24 h. The aqueous mixture was added to a FluoroFlash® silica gel column (2 cm × 30 cm), and **4a** was obtained as a pure product by gradient elution using acetone–water. Subsequently, compound **1** was reacted with various aldehydes **3** under the standard aqueous indium-mediated allylation protocol (Table 1).[8] Upon simple filtration through a short plug of fluorous silica gel, the corresponding allylation products **4** were obtained cleanly without need for further purification.

Consistent with other studies on Barbier–Grignard-type reactions in water, aromatic aldehydes (Table 1, entries 1, 3–6) generally gave higher yields of the corresponding allylation products than aliphatic aldehydes (Table 1, entries 7 and 8), with the exception of fluorinated aromatic aldehydes (Table 1, entry 2). At the present time, it is not clear what caused the lower yields of the fluoroaromatic aldehydes.

On the other hand, the reaction of reagent **2** with various aldehydes generated the corresponding esters **5** (Table 2).[9] Further treatment of the esters with base generated the α-methylene-γ-butyrolactones **6** in high yields.[10] Surprisingly, only trace amounts of the lactones were obtained with *ortho*-substituted aryl aldehydes, most likely due to steric reasons (Table 2, entries 4 and 5). It should be noted that a water-soluble aldehyde also reacted to give the desired product (Table 2, entry 10), albeit with a low conversion, and requiring a modification of the conditions for the allylation step.

In conclusion, an isolation technique has been developed for directly separating product mixtures of aqueous indium-mediated allylations by using the fluorous-tag method. Various aldehydes were transformed into the desired products and isolated in pure form readily by this method. The fluorous tag regenerated in pure form from the FluoroFlash® silica gel column can be reused for further reactions.

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Notes and references

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2 M. Wende, R. Meier and J. A. Gladysz, *J. Am. Chem. Soc.*, 2001, **123**, 11490.
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5 C.-J. Li and T. H. Chan, *Tetrahedron Lett.*, 1991, **32**, 7017.
6 C.-J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149; C.-J. Li and T. H. Chan, *Comprehensive Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 2007; C.-J. Li, in *Organic Synthesis in Water*, ed. U. M. Lindstrom, Blackwell, New York, 2007.
7 Synthesis of **1**: A solution of 1*H*,1*H*-perfluorohexan-1-ol (2.4 g, 8.0 mmol) in dry THF (20 mL) was added slowly over 10 min to a stirred solution of sodium hydride (0.23 g, 9.7 mmol) in dry THF (20 mL) at room temperature. The mixture was stirred at rt for 30 min, then 3-chloro-2-chloromethyl-1-propene (1.5 g, 12 mmol) was added and stirred for 6 h. The reaction mixture was quenched with ice–water, extracted with diethyl ether (3 × 20 mL), and the combined extracts were dried and concentrated *in vacuo.* Column chromatography of the residue on silica using hexane–diethyl ether (50 : 1) as eluent gave **1** (1.72 g, 55%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 Hz): δ (ppm) 5.30 (s, 1H), 5.21 (s, 1H), 4.17 (s, 2H), 4.03 (s, 2H), 3.88 (t, J = 14 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ (ppm) 140.8, 118.3, 72.8, 67.3 (t, OCH_2, $J_{C\text{-}F}$ = 26 Hz), 44.8; GC–MS *m*/*z* (relative intensity): 388 (M^+, 5), 177 (25), 141 (100), 113 (35), 77 (65), 51 (20). Synthesis of **2**: To a mixture of 2-(bromomethyl)acrylic acid (5.0 g, 0.03 mol) and 1*H*,1*H*-perfluorohexan-1-ol (15.0 g, 0.05 mol), concentrated sulfuric acid (1.0 g) was added slowly and the mixture then stirred at 50 °C for 15 min. The mixture was heated at 130 °C for 6 h. After workup, flash chromatography on silica using hexane–ethyl acetate (20 : 1) as eluent gave the ester **2** (8.7 g, 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm): 6.41 (s, 1H), 6.08 (s, 1H), 4.69 (t, J = 13.6 Hz, 2H), 4.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 136.2, 131.4, 60.4 (t, OCH_2 $J_{C\text{-}F}$ = 27.5 Hz), 28.5; ^{19}F NMR ($CDCl_3$, C_6F_6 −164.9 ppm, 376 MHz): δ (ppm) −83.98 (3F), −122.64 (2F), −126.22 (2F), −126.71 (2F), −129.47 (2F); GC–MS *m*/*z* (relative intensity): 447 (M^+, 65), 367 (100), 147 (45); IR (liquid film): ν_{max} 3000, 1750 cm^{-1}.
8 A mixture of benzaldehyde (48 mg, 0.45 mmol), **1** (117 mg, 0.30 mmol) and indium powder (52 mg, 0.45 mmol) in 4 mL water was stirred at 50 °C in air for 24 h. The aqueous mixture was added to a FluoroFlash® silica gel (FluoroFlash® silica gel bonded with perfluorooctylethylsilyl chains, 40 μm, 60 Å particle size from Fluorous Technologies Inc.) column (2 cm × 30 cm) and **4a** was obtained by gradient eluention [acetone–water in ratios of 50 : 50 (100 mL), 70 : 30 (20 mL) and 80 : 20] as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 Hz): δ (ppm) 7.38–7.26 (m, 5H), 5.20 (s, 1H), 5.12 (s, 1H), 4.84 (dd, J = 5.2, 8.4 Hz, 1H), 4.12 (d, J = 12 Hz, 1H), 4.03 (d, J = 12.4 Hz, 1H), 3.89 (t, J = 12.4 Hz, 2H), 2.52 (dd, J = 4.8, 14.4 Hz, 1H) 2.47 (dd, J = 8.4 12.4 Hz, 1H), 2.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.2, 141.4, 128.7, 127.9, 125.9, 117.3, 75.8, 72.8, 66.9 (t, OCH_2, $J_{C\text{-}F}$ = 25.9 Hz), 43.5.
9 To a mixture of benzaldehyde (48 mg, 0.45 mmol) and **2** (135 mg, 0.30 mmol) in 4 mL water, indium powder (52 mg, 0.45 mmol) was added and the mixture was stirred at rt in air for 24 h. The crude reaction mixture was added to a FluoroFlash® silica gel column, and washed with 100 mL of acetone–water (50 : 50) and 60 mL acetone–water (70 : 30). An 80 : 20 mixture of acetone and water eluted the desired product **5a**. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm): 7.34–7.26 (m, 5H), 6.34 (s, 1H), 5.73 (s, 1H), 4.87 (dd, J = 4.4, 8.4 Hz, 1H), 4.68–4.59 (m, 2H), 2.78 (ddd, J = 1.2, 4.4, 14 Hz, 1H), 2.70 (ddd, J = 0.8, 8.4, 14.4 Hz, 1H), 2.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 143.8, 135.6, 130.9, 128.7, 128.0, 125.9, 73.1, 60.2 (O–CH_2, t, J = 26.7 Hz), 42.2; ^{19}F NMR ($CDCl_3$, C_6F_6 −164.9, 376 MHz): δ (ppm) −83.97(3F), −117.98 (1F), −122.62 (2F), −126.20 (2 F), −129.47; IR (liquid film): ν_{max} 3500–3250, 3050, 2900, 1750 cm^{-1}.
10 Representative example for the preparation of α-methylene-γ-butyrolactones: Diethyl ether (2 mL) was added to 4-hydroxy-2-methylene-4-phenyl-butyric acid 2,2,3,3,4,4,5,5,6,6,6-undecafluoro-hexyl ester **5a** (139 mg, 0.30 mmol) and K_2CO_3 (2 mg, 5 mol%) and the solution was stirred at rt in air for 24 h. The ether was then removed and the residue was diluted with hexane and transferred on to a column. The desired product **6a** was eluted with hexane–ethyl acetate 10 : 1 to give a white solid (52 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39–7.28 (m, 5H), 6.26 (t, J = 3.2 Hz, 1H), 5.67 (t, J = 2.4 Hz, 1H), 5.50 (dd, J = 6.8, 6.8 Hz, 1H), 3.38 (ddt, J = 2.8, 8, 17.2 Hz, 1H), 2.89 (ddt, J = 2.8, 6.4, 17.2 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 170.5, 140.0, 134.4, 129.1, 128.8, 125.6, 122.8, 78.2, 36.5.