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# Direct Use of Esters in the Mukaiyama Aldol Reaction: A Powerful and Convenient Alternative to Aldehydes

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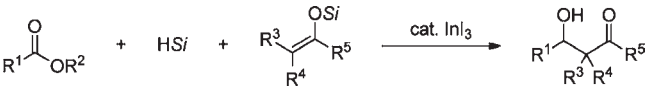
## ABSTRACT




**An indium triiodide catalyst promoted the direct transformation from esters to β-hydroxycarbonyl compounds using hydrosilanes and silyl enolates by a one-stage process. Various esters were applicable, and the high chemoselectivity of this system brings compatibility to many functional groups: alkenyl, alkynyl, chloro, and hydroxy.**

The cross-aldol reaction is one of the most representative tools in organic chemistry because produced β-hydroxycarbonyl compounds play an important role in medicinal and agricultural chemicals. In particular, the Mukaiyama aldol reaction using aldehydes and silyl enolates is of central importance.[1] While aldehydes are versatile electrophiles, some have problems with stability and storage. In this context, we sought to combine esters and hydrosilanes instead of aldehydes, where the simple treatment of both reagents and silyl enolates in the presence of a catalyst would achieve a Mukaiyama aldol addition (Figure 1). Yet, the scarcity of reports on the selective hydrosilylation of esters into aldehydes under catalytic conditions indicates the difficulty of this alternative route using esters.[2] Recently, the $InBr_3$-catalyzed hydrosilylation of esters into the corresponding ethers via no formation of aldehydes was investigated.[3] Even in the case of an active metal hydride, there is only one example of the use of DIBALH. However, a two-stage process, where the completion of the DIBALH addition to esters was followed by a treatment with silyl enolates, was required.[4a] Recently, we reported some examples of the removal of the alkoxy moiety of esters: hydroallylation[5] and Friedel–Crafts acylation.[6] In particular, part of the hydroallylation results strongly suggested that esters would be a promising alternative to aldehydes. Herein, we wish to report the direct synthesis of β-hydroxycarbonyl compounds from esters, hydrosilanes, and silyl enolates, developing a practical alternative to the Mukaiyama aldol reaction using aldehydes. This system does not require a multistage process.

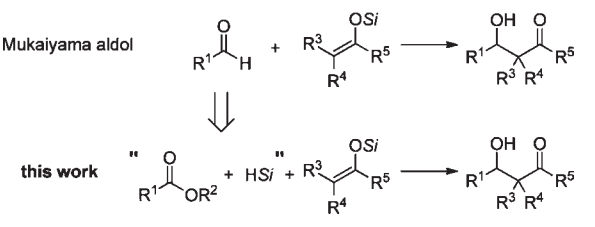



**Figure 1.** A conceivable strategy in this paper.

(1) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011–1014. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509. (c) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1, p 2.

(2) (a) Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 2149–2151. (b) Nakanishi, J.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Synlett* **2006**, 869–872. (c) Ojima, I.; Kumagai, M.; Nagai, Y. *J. Organomet. Chem.* **1976**, *111*, 43–60. For reduction of carboxylic acids and carboxylic acid derivatives to aldehydes, see: (d) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051. (e) Kimura, M.; Seki, M. *Tetrahedron Lett.* **2004**, *45*, 3219–3223. (f) Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, *14*, 619–620. (g) Kim, M. S.; Choi, Y. M.; An, D. K. *Tetrahedron Lett.* **2007**, *48*, 5061–5064. (h) Nahm, S.; Weinreb, M. *Tetrahedron Lett.* **1981**, *39*, 3815–3818.

(3) Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5920–5922.

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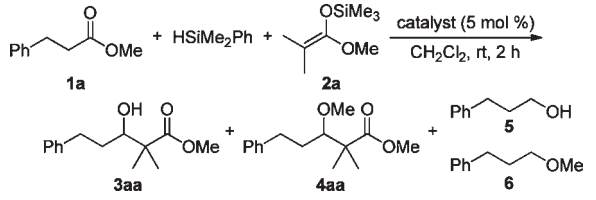
The reaction using methyl ester **1a** (1 mmol), $HSiMe_2Ph$ (1.5 mmol), and dimethylketene trimethylsilyl methyl acetal **2a** (1.5 mmol) in $CH_2Cl_2$ at rt was most effectively catalyzed by $InI_3$ to give the desired $\beta$-hydroxycarbonyl compound **3aa** in 92% yield with a negligible amount of $\beta$-methoxycarbonyl compound **4aa** (Table 1, entry 1). The use of $InBr_3$ catalyst produced a low yield (entry 2). The higher Lewis acidity of $InBr_3$ than that of $InI_3$ lowers the turnover frequency because of the stronger deactivation by the coordination of O-atoms of starting materials and products. Almost the entire amount of starting ester **1a** was unreacted in the runs using other indium compounds (entries 3−5). Also, representative Lewis acids such as $BF_3\cdot OEt_2$ and $AlCl_3$ were ineffective.[7] In the case of $Ti(OiPr)_4$,[8] $B(C_6F_5)_3$,[9] and $Zn(OAc)_2$,[10] which have reportedly reduced esters using hydrosilane, the desired product **3aa** was not gained efficiently (entries 6−8). In the case of the $InI_3$ catalyst, the salient features are as follows: (i) the produced ester **3aa** did not incur further nucleophilic additions; (ii) despite one-stage treatment, no generation of the reduction products **5** and **6** was observed, which is a critical problem in the hydroallylation of esters;[5,11] and (iii) the lack of formation of ether derivatives such as **4aa** and **6** provided an interesting contrast to the reduction of esters to ethers with the $InBr_3/HSiEt_3$ system reported by Sakai.[3]

Table 2 summarizes the scope and limitation of applicable esters **1**. The present system is highly valuable as an alternative for the Mukaiyama aldol reaction, because esters **1b** and **1c**, corresponding to acetaldehyde and phenylacetaldehyde, respectively, were applicable (entries 1 and 2). In general, these aliphatic aldehydes are labile and too difficult to handle.[12] The product **3da** was also isolated in 92% yield from the reaction using ester **1d** possessing a cyclohexyl group near the carbonyl moiety (entry 3). In the case of the sterically hindered ester **1e**, a good result was obtained by using $H_3SiPh$ instead of $HSiMe_2Ph$ (entries 4 and 5). The reaction of methyl benzoate **1f** resulted in a low yield due to the low electrophilicity of aromatic esters (entry 6). The transformation of ester **1g** gave **3ga** with a

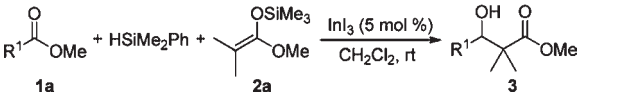
**Table 1.** Reaction of Ester **1a** with $HSiMe_2Ph$ and Ketene Silyl Acetal **2a** in the Presence of Lewis Acid Catalyst[a]

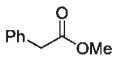
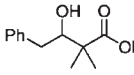
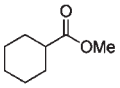
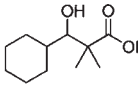
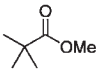
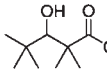
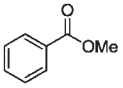
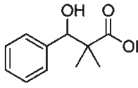
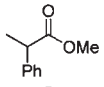
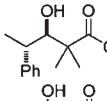
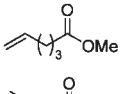
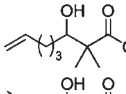
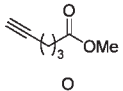
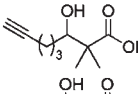
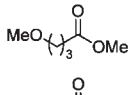
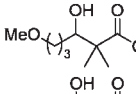
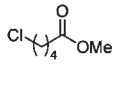
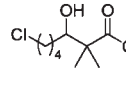



| | | yield/ %[b] | | | |
|---|---|---|---|---|---|
| entry | catalyst | **3aa** | **4aa** | **5** | **6** |
| 1 | $InI_3$ | 92 | 1 | 0 | 0 |
| 2 | $InBr_3$ | 17 | 1 | 0 | 0 |
| 3[c] | $InCl_3$ | 0 | 0 | 0 | 0 |
| 4[c] | $In(OTf)_3$ | 0 | 0 | 0 | 0 |
| 5[c] | $In(OH)_3$ | 0 | 0 | 0 | 0 |
| 6[c] | $Ti(OiPr)_4$ | 0 | 0 | 0 | 0 |
| 7 | $B(C_6F_5)_3$ | 17 | 0 | 45 | 0 |
| 8[c] | $Zn(OAc)_2$ | 0 | 0 | 0 | 0 |

[a] Reaction conditions: **1a** (1 mmol), $HSiMe_2Ph$ (1.5 mmol), **2a** (1.5 mmol), catalyst (0.05 mmol), $CH_2Cl_2$ (1 mL), rt, 2 h. [b] Yields were determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] > 90% of **1a** was recovered.

**Table 2.** Scope and Limitation of Esters **1**[a]




| entry | ester **1** | | product **3** | | yield / %[b] |
|---|---|---|---|---|---|
| 1 |  | **1b** |  | **3ba** | 53 (83[c]) |
| 2 |  | **1c** |  | **3ca** | 69 |
| 3 |  | **1d** |  | **3da** | 92 |
| 4[d] |  | **1e** |  | **3ea** | 6[c] |
| 5[e] | | **1e** | | **3ea** | 60 |
| 6[e] |  | **1f** |  | **3fa** | 23 |
| 7[f] |  | **1g** |  | **3ga** | 79[g] |
| 8 |  | **1h** |  | **3ha** | 55 |
| 9[f] |  | **1i** |  | **3ia** | 55 |
| 10 |  | **1j** |  | **3ja** | 80 |
| 11 |  | **1k** |  | **3ka** | 76 |

[a] Reaction conditions: **1** (1 mmol), $HSiMe_2Ph$ (1.5 mmol), **2a** (1.5 mmol), $InI_3$ (0.05 mmol), $CH_2Cl_2$ (1 mL), rt, 2 h. [b] Isolated yield. [c] Yield was determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [d] $HSiMe_2Ph$ (3 mmol), **2a** (3 mmol), 12 h. [e] $H_3SiPh$ (3 mmol), **2a** (3 mmol), 12 h. [f] $HSiMe_2Ph$ (2 mmol), **2a** (2 mmol), 5 h. [g] *anti*/*syn* = 92:8.

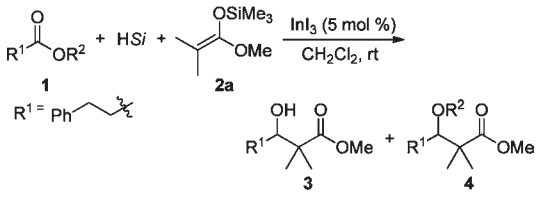
(4) (a) Kiyooka, S.; Shirouchi, M. *J. Org. Chem.* **1992**, *57*, 1–2. For the use of DIBAL and other nucleophiles with esters, see: (b) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469–5480. (c) Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905–3906. (d) Ishihara, T.; Hayashi, H.; Yamanaka, H. *Tetrahedron Lett.* **1993**, *34*, 5777–5780. (e) Ishihara, T.; Takahashi, A.; Hayashi, H.; Yamanaka, H.; Kubota, T. *Tetrahedron Lett.* **1998**, *39*, 4691–4694. (f) Hove, T. H.; Kopel, L. C.; Ryda, T. D. *Synthesis* **2006**, 1572–1574. (g) Yamazaki, T.; Kobayashi, R.; Kitazume, T.; Kubota, T. *J. Org. Chem.* **2006**, *71*, 2499–2502.

high *anti*-diastereoselectivity (entry 7). Alkenyl, alkynyl, methoxy, and chloro groups survived the conditions (entries 8–11). The above-mentioned outcomes suggest that the high chemoselectivity of this work can be applied to various fields such as natural-product synthesis.[13]

The effects of alkoxy moieties of ester **1** and hydrosilanes (H*Si*) were investigated in Table 3. Unlike the exclusive formation of **3aa** using methyl ester **1a**, the reaction of isopropyl ester **1l** with $HSiMe_2Ph$ and ketene silyl acetal **2a** furnished the mixture of $\beta$-hydroxycarbonyl product **3aa** and $\beta$-isopropoxycarbonyl **4la** in 89% and 11% yields, respectively (entries 1 and 2). The ratio was almost reversed by the usage of $H_3SiPh$ to produce the mixtures of **3aa** and **4la** in 20% and 80% yields, respectively (entry 3). In contrast, **1a** provided $\beta$-hydoxycarbonyl product **3aa** selectively even in the case of $H_3SiPh$ (entry 5). Treatment of $HSiEt_3$ and **1a** gave **3aa** along with a negligible amount of **4aa** (entry 6). Ethyl ester **1m** also showed high selectivity for $\beta$-hydroxycarbonyl product **3aa** (entries 7 and 8). These results suggested that a small alkoxy moiety leads to the selective formation of $\beta$-hydoxycarbonyl compound **3**.

A plausible mechanism is illustrated in Scheme 1. First, $InI_3$-catalyzed hydrosilylation of methyl ester **1** takes place to generate acetal intermediate **7**.[3,5] Next, the selective interaction between $InI_3$ and the methoxy moiety promotes the elimination of the methoxy moiety, due to a less steric hindrance, to afford either oxonium ion **8** or aldehyde **9**. Finally, the reaction with silyl enolate **2** produces $\beta$-siloxycarbonyl compound **10**, along with the regeneration of $InI_3$.[14] The effective nucleophilic attack of **2** in a timely manner may prevent the reduction of the electrophilic intermediate (**8** or **9**) by hydrosilane to achieve a single treatment of all substrates. The stereochemistry of **3ga** was well accounted for by the Felkin–Anh model for oxonium cation **8** or aldehyde **9** (Table 2, entry 7).[15]

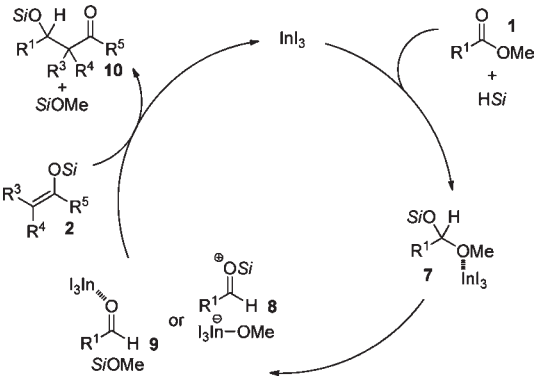
**Table 3.** Effects of Alkoxy Moieties of Ester **1** and Hydrosilanes[a]




| entry | ester **1** | | | H*Si* | products/ %[b] **3** | **4** |
|---|---|---|---|---|---|---|
| 1 | $R^2$ = | Me | **1a** | $HSiMe_2Ph$ | 92 | 1 |
| 2 | | *i*Pr | **1l** | $HSiMe_2Ph$ | 89 | 11 |
| 3 | | *i*Pr | **1l** | $H_3SiPh$ | 20 | 80 |
| 4 | | *i*Pr | **1l** | $HSiEt_3$ | 52 | 5 |
| 5 | | Me | **1a** | $H_3SiPh$ | 75 | 7 |
| 6 | | Me | **1a** | $HSiEt_3$ | 90 | 1 |
| 7 | | Et | **1m** | $HSiMe_2Ph$ | 83 | 1 |
| 8 | | Et | **1m** | $HSiEt_3$ | 81 | 2 |

[a] Reaction conditions: **1** (1 mmol), H*Si* (1.5 mmol), **2a** (1.5 mmol), $InI_3$ (0.05 mmol), $CH_2Cl_2$ (1 mL), rt, 2 h. [b] Yields were determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

**Scheme 1.** Plausible Mechanism




The one-step transformation from mandelic acid ester **1n** to $\beta$-hydroxy-$\gamma$-lactone **12** with high stereoselectivity was

(5) Nishimoto, Y.; Inamoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2010**, 3382–3386.

(6) Nishimoto, Y.; Babu, S. A.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2008**, *73*, 9465–9468.

(7) See Supporting Information for the investigation of typical Lewis acids.

(8) (a) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751–3753. (b) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1995**, *60*, 7884–7890.

(9) (a) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440–9441. (b) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090–3098.

(10) Das, S.; Möller, K.; Junge, K.; Beller, M. *Chem.—Eur. J.* **2011**, *17*, 7417–7417.

(11) The reaction of esters with hydrosilanes and allylsilanes in the presence of $InI_3$ catalyst produced the mixture of homoallylic alcohol and primary alcohol in a single treatment. A drop treatment for hydrosilane should be required to selectively obtain homoallylic alcohol. See ref 5.

(12) Ariza, X.; Asins, G.; Garcia, J.; Hegardt, F. G.; Makowski, K.; Serra, D.; Velasco, J. *J. Label. Radiopharm.* **2010**, *53*, 556–558.

(13) For examples of the total synthesis in which the reduction of a carboxylic acid derivative to aldehyde followed by the Mukaiyam aldol reaction was carried out, see: (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513. (b) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2741–2744. (c) Trost, B. M.; Sieber, J. D.; Qian., W.; Dhawan, R.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 5478–5481.

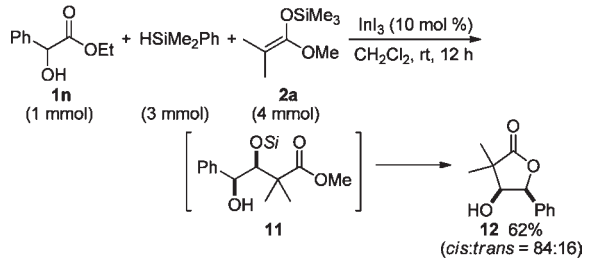
(14) The transformation from **10** to $\beta$-hydroxycarbonyl compound **3** is performed by TBAF in the post-treatment.

(15) (a) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667–1668. (b) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107–6115. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192 and references therein.

(16) Since $\beta$-hydroxy-$\gamma$-lactones are key intermediates in the synthesis of natural products, a large number of studies have reported their preparation; see: (a) Nacro, K.; Gorrichon, L.; Escudier, J.-M.; Baltas, M. *Eur. J. Org. Chem.* **2001**, 4247–4258. (b) Karisalmi, K.; Koskinen, A. M. P. *Synthesis* **2004**, *9*, 1331–1342. (c) Ghosh, A. K.; Kass, J.; Anderson, D. D.; Xu, X.; Marian, C. *Org. Lett.* **2008**, *10*, 4811–4814.

(17) $\beta$-Hydroxy-$\gamma$-lactone was prepared from the protected α-hydroxy aldehydes by the Mukaiyama aldol reaction; see: (a) Kiyooka, S.; Kira, H.; Hana, M. A. *Tetrahedron Lett.* **1996**, *37*, 2597–2600. (b) Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Kishino, H.; Ke, Y. Y.; Tamura, Y. *J. Org. Chem.* **1988**, *53*, 554–561.

**Scheme 2.** One-Step Transformation from Mandelic Acid Ester **1n** to $\beta$-Hydroxy-$\gamma$-lactone **12**



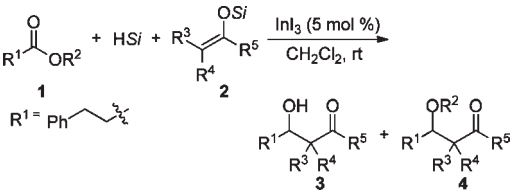

demonstrated (Scheme 2).[16] In the case of the Mukaiyama aldol reaction, multistep syntheses involving protection of the hydroxy moiety in unstable α-hydroxyaldehydes should be performed.[17] The stereochemistry of product **12** was explained by the Cram chelate model of 1,2-induction in the reaction of the corresponding intermediate such as oxonium cation **8** or aldehyde **9** with ketene silyl acetal **2a**.[18]

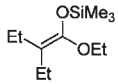
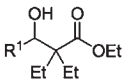
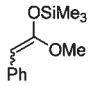
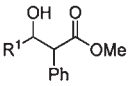
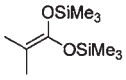
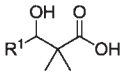
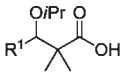
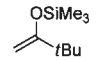
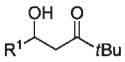
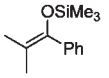
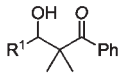
Table 4 shows the scope of silyl enolates **2**. Diethyl- and phenylketene silyl acetal (**2b** and **2c**) applied well to the present system (entries 1 and 2). The reaction of carboxylic acid derived ketene silyl acetal **2d** also furnished $\beta$-hydroxycarboxylic acid **3ad** in high yields (entry 3). The utilization of **1l**, $H_3SiPh$, and **2d** resulted in $\beta$-isopropoxycarboxylic acid **4ld** as a major product (entry 4). The employment of silyl enol ethers is a challenging subject because the produced $\beta$-oxyketone is more sensitive to nucleophilic attack than starting esters. This issue was resolved by the introduction of $HSiMePh_2$ and silyl enol ethers such as **2e** and **2f**, leading to the products **3ae** and **3af** possessing steric hindrance around the carbonyl group to avoid overreaction (entries 5 and 6).

In conclusion, we have established the first direct introduction of esters into the Mukaiyama aldol reaction catalyzed by $InI_3$. Various types of esters and silyl enolates were applicable, and the high chemoselectivity lent compatibility to many functional groups. In addition, we demonstrated the replacement of unstable and difficult to handle aldehydes such as acetaldehyde, phenylacetaldehyde, and an α-hydroxyaldehyde with the corresponding esters.

(18) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748–2755. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462–468 and references therein.

**Table 4.** Scope and Limitation of Silyl Enolates **2**[a]




| entry | Silyl enolate **2** | | product **3** or **4** | | yield / %[b] |
|---|---|---|---|---|---|
| 1 |  | **2b** |  | **3ab** | 69 |
| 2 |  | **2c**[c] |  | **3ac** | 94[d] |
| 3 |  | **2d** |  | **3ad** | 69 |
| 4[e] | | **2d** |  | **4ld** | 75[f] |
| 5[g] |  | **2e** |  | **3ae** | 30 |
| 6[g] |  | **2f** |  | **3af** | 34 |

[a] Reaction conditions: **1a** (1 mmol), $HSiMe_2Ph$ (1.5 mmol), **2a** (1.5 mmol), $InI_3$ (0.05 mmol), $CH_2Cl_2$ (1 mL), rt, 2 h. [b] Isolated yields. [c] $E/Z$ = 76:24 [d] Diastereomer ratio 53:47. [e] **1l** (1 mmol), $H_3SiPh$ (1.5 mmol). [f] **3ad** was obtained in 19% yield determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [g] $HSiMePh_2$ (3 mmol), **2** (3 mmol), 5 h.

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**Supporting Information Available.** Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.