# Indium hydride catalyzed chemo- and diastereoselective reductive aldol reactions

Ryosuke Ieki, Shinji Miyamoto, Shinji Tsunoi, Ikuya Shibata*

*Research Center for Environmental Preservation, Osaka University, 2-4 Yamadaoka, Suita, Osaka 565-0871, Japan*

A B S T R A C T

The reductive aldol reaction of enones has been established catalyzed by $Br_2InOMe$ (cat.)−$MePhSiH_2$ system where $Br_2InH$ acted as an active catalytic species. Addition of 1.0 equivalent of MeOH was essential for catalytic turnover. The system, $Br_2InOMe$(cat.)−$MePhSiH_2$−MeOH, provided highly chemo- and diastereoselective reductive aldol reaction of enones with functionalized substrates such as α-bromo carbonyls, α-keto esters and α-alkoxy ketones.

© 2013 Elsevier B.V. All rights reserved.

## 1. Introduction

The reductive aldol reaction of enones with aldehydes promoted by metal hydrides is a valuable method for obtaining β-hydroxyketones in one-pot synthesis [1]. To date, metal-catalyzed reductive aldol reaction of enones has been investigated [2]. We have previously reported that dibromoindium hydride ($Br_2InH$) as stoichiometric metal hydride promoted reductive aldol reaction of enones with aldehydes [3]. Moreover, catalytic generation of indium hydride species was successful by $InBr_3$(cat.)−$Et_3SiH$ [4a] and $In(OAc)_3$(cat.)−$PhSiH_3$ systems [4b]. Although $InBr_3$(cat.)−$Et_3SiH$ underwent highly diastereoselective reactions [4a], functionalized substrates were not applicable because of accompanying an acidic by-product $Et_3SiBr$ in the transmetallation. We have developed a mild method for generating $Br_2InH$ by using $Br_2InOMe$ instead of $InBr_3$ and applied to radical cyclization of functionalized substrates [5]. We report here the catalytic reductive aldol reaction of enones by $Br_2InOMe$(cat.)−hydrosilane system, and accomplished high chemo- and diastereoselectivities (Scheme 1).

## 2. Results and discussion

To optimization of conditions for the indium-catalyzed reductive aldol reaction, initially, we performed the simple example of 1- phenyl-2-buten-1-one (**1**) with cyclohexanone (**2a**) in the presence of a catalytic amount of $Br_2InOMe$ and stoichiometric $MePhSiH_2$ (Table 1). Without additives, no aldol product **3a** was obtained at rt for 3 h (entry 1). When MeOH was used as an additive, product **3a** was obtained (entry 2). However, undesirable side product, 1-phenyl-butan-1-one, was formed by conjugate reduction of 1 in 84% yield. The reaction at lower temperature provided a maximum yield of **3a** (52%) (entry 3). Yields were not satisfactory when $H_2O$ or $^iPrOH$ was used in place of MeOH (entries 4 and 5). The use of $Ph_2SiH_2$ as a hydride source slightly decreased the yield of **3a** (entry 6). $PhSiH_3$ and $Et_3SiH$ were not effective as stoichiometric reductants (entries 7 and 8).

A plausible catalytic cycle is shown in Scheme 2. Initially, $Br_2InH$ is formed by the transmetallation of $Br_2InOMe$ with $MePhSiH_2$. $Br_2InH$ undergoes conjugate reduction to enone **1** to give indium enolate **A** [6]. In this step, $Br_2InH$ could reduce ketone **2a**. The conditions at 0 °C allows the predominant reduction of enone **1**. Next, generated indium enolate **A** reacts with ketone **2a** to form indium aldolate **B**. In the final step, aldolate **B** is protonated by MeOH, and aldol product **3a** is obtained with regeneration of $Br_2InOMe$. We assume that this is the rate determining step. The choice of additive is important. Thus MeO group has effects on both steps of trapping of indium aldolate **B** and of generation of $Br_2InH$. Using $^iPrOH$ instead of MeOH does not promote protonation of indium aldolate and generation of $Br_2InH$ due to less acidity and generation of sterically hindered indium alkoxide compared with MeOH.

We next tried to use functionalized substrates. In the reaction with α-bromo alkylaldehyde **2b**, desired product **3b** was obtained

---

* Corresponding author. Tel.: +81 6 6879 8975; fax: +81 6 6879 8978.
E-mail address: shibata@epc.osaka-u.ac.jp (I. Shibata).
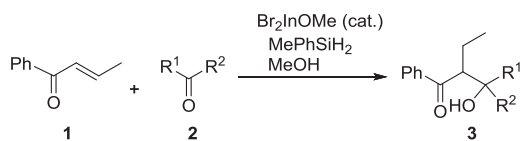
Scheme 1. Reductive aldol reaction of enones.

in 40% yield (Scheme 3). Noteworthy is high diastereoselectivity of the reaction via Zimmerman–Traxler six-membered transition state C [7]. Previously reported system, InBr$_3$(cat.)–Et$_3$SiH, resulted in low yield. Thus in the generation of Br$_2$InH, InBr$_3$(cat.)–Et$_3$SiH system [4a] accompanied acidic Et$_3$SiBr which would decompose functionalized compounds, 2b and 3b. In contrast, starting from Br$_2$InOMe–MePhSiH$_2$ accompanied silyl methoxide as a mild and neutral by-product.

The reactions using other functionalized ketones are summarized in Table 2. The highly chemoselective reaction was also applicable to α-bromo acetophenone (2c) (entry 2). The presented reductive aldol reaction has limited application for simple ketone such as acetophenone. However, dehalogenation of product 3c afforded adduct 4 which corresponds to the product using acetophenone (Scheme 4).

Functionalized ketones such as α-keto esters, 2d and 2e, were also reactive to give products, 3d and 3e, respectively (entries 2 and 3). No by-products derived from the reduction of 2d and 2e were obtained. Noteworthy is high diastereoselectivities of these reactions which could be rationalized by bicyclic transition state D as shown in Scheme 5.

The use of α-methoxy acetophenone 2f also underwent highly diastereoselective reaction where OMe group acts as coordinating group to indium (entry 4). The reaction with benzoin methyl ether (2g) gave diastereoselective product 3g with three contiguous stereogenic centers (entry 5). In this reaction, among possible chelated cyclic transition states, an excellent stereocontrol was achieved through E as sterically least hindered cyclic transition state (Scheme 6).

## 3. Conclusions

We have established that MePhSiH$_2$ and MeOH promoted reductive aldol reaction of enones in the presence of a catalytic amount of dibromoindium methoxide (Br$_2$InOMe). Br$_2$InH acted as an active catalytic species. The reactions were performed only using main group metals and any expensive transition metals were not

Table 1
Optimization of reductive aldol reaction of enone 1 with 2a.[a]
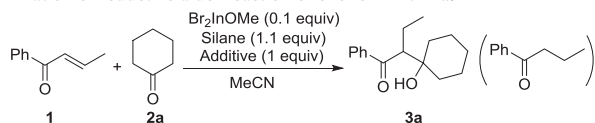


| Entry | Silane | Conditions | Additive | 3a Yield%[b] |
|---|---|---|---|---|
| 1 | MePhSiH$_2$ | rt, 3 h | None | Trace (5) |
| 2 | MePhSiH$_2$ | rt, 3 h | MeOH | 12 (84) |
| 3 | MePhSiH$_2$ | 0 °C, 24 h | MeOH | 52 (37) |
| 4 | MePhSiH$_2$ | 0 °C, 24 h | H$_2$O | Trace (15) |
| 5 | MePhSiH$_2$ | 0 °C, 24 h | $^i$PrOH | Trace (14) |
| 6 | Ph$_2$SiH$_2$ | 0 °C, 24 h | MeOH | 37 (26) |
| 7 | PhSiH$_3$ | 0 °C, 24 h | MeOH | 10 (72) |
| 8 | Et$_3$SiH | 0 °C, 24 h | MeOH | Trace (trace) |

[a] Conditions: Br$_2$InOMe (0.1 mmol), silane (1.1 mmol), additive (1.0 mmol), 1 (1 mmol), 2a (1 mmol), MeCN (1 mL).
[b] Yields of 1-phenyl-butan-1-one in parentheses.
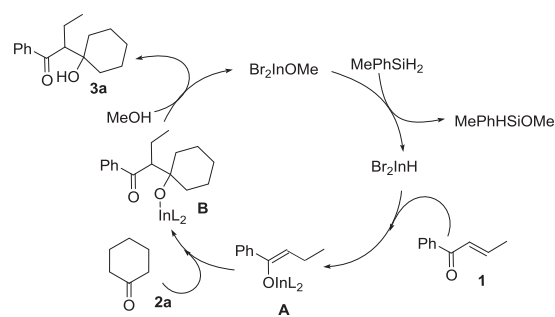


Scheme 2. Plausible catalytic cycle.

required. Highly chemo- and diastereoselective aldol products were obtained in the case using α-halo ketones, α-keto esters and α-alkoxy ketones. We are now enlarging the scope of substrates.

## 4. Experimental

### 4.1. General experimental methods

To a dry nitrogen-filled 10-mL round-bottomed flask containing InBr$_3$ (0.1 mmol) in MeCN (1 mL) was added NaOMe (0.12 mmol) at rt. The mixture was stirred at room temperature for 30 min. To the solution were added MePhSiH$_2$ (1.1 mmol), enones 1 (1 mmol), carbonyl 2 (1 mmol) and MeOH (1 mmol) and the resulting mixture was stirred at 0 °C for 24 h. After quenching with saturated NaCl (aq) (2 mL), the reaction mixture was extracted with ether (10 mL × 2). The combined organic layer was dried over MgSO$_4$ and concentrated. The residue was subjected to column chromatography eluting with hexane/EtOAc. Indium and silane residue were removed by this treatment. The crude product was then purified by flash column chromatography eluted by hexane/EtOAC with gradation mode changing from 9/1 to 3/7. The desired product was obtained at hexane/EtOAC = 7:3.

### 4.1.1. 2-(1′-Hydroxy-cyclohexyl)-1-phenyl-butan-1-one (3a)

The NMR data well agree with the reported data in Ref. [2i].
Colorless liquid. IR (neat) 3493 cm$^{-1}$ (OH), 1659 cm$^{-1}$ (C=O). MS (EI, 70 eV) m/z 246 (M$^+$, 5), 105 (PhCO, 100), 77 (Ph, 28). HRMS calcd for C$_{16}$H$_{22}$O$_2$: 246.1620, found: m/z 246.1614 (EI, M$^+$, −0.6 mmu). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.00–7.98 (m, 2H, Ph(o)), 7.62–7.57 (m, 1H, Ph(p)), 7.51–7.47 (m, 2H, Ph(m)), 3.51 (dd, J = 4.3 and 9.9 Hz, 1H, C=OCH), 3.47 (s, 1H, OH), 1.93–1.18 (m, 12H, CH$_2$Me, cyclohexyl CH$_2$), 0.83 (t, J = 7.48 Hz, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 208.6, 138.9, 133.4, 128.7, 128.2, 73.0, 54.7, 37.7, 35.2, 25.7, 21.8, 21.7, 20.9, 12.7.

### 4.1.2. 4-Bromo-2-ethyl-3-hydroxy-1, 5-diphenyl-pentan-1-one (3b)

Pale yellow liquid. IR (neat) 3444 cm$^{-1}$ (OH), 1651 cm$^{-1}$ (C=O). MS (CI, 200 eV) m/z 362 (M$^+$ + 1, 20.38). HRMS calcd for
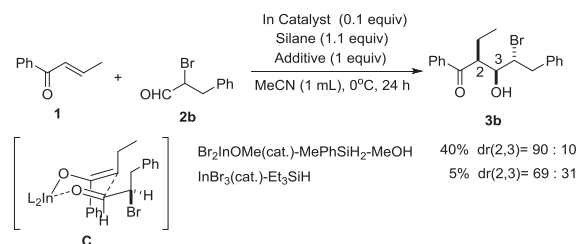


Scheme 3. The reaction of 1 with α-bromo alkylaldehyde (2b).