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An efficient indium-mediated 2-bromoallylation of aldehydes at low temperature in aqueous DMF

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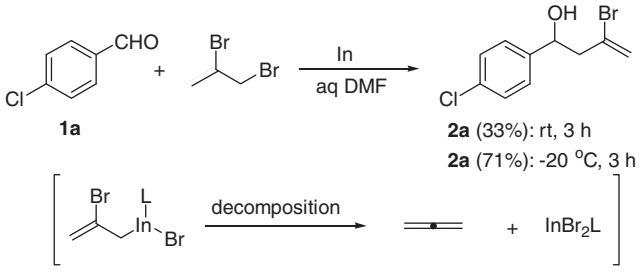
ABSTRACT

An efficient synthesis of 2-bromohomoallylic alcohols was carried out via an indium-mediated Barbier-type 2-bromoallylation of aldehydes in moderate yields. The reaction was performed at low temperature (−20 °C) in aqueous DMF in order to minimize decomposition of 2-bromoallylindium reagent to allene.

2-Bromoallylation of carbonyl compounds to 2-bromohomoallylic alcohols has been the subject of current interest.[1–5] 2-Bromohomoallylic alcohols have been used for the synthesis of various important substances including 2-methyleneoxetanes,[1c] homopropargylic alcohols,[1e] 2-methyleneazetidines,[1f] and α-methylene-γ-butyrolactones.[1a,3a,c] However, 2-bromoallylation of carbonyl compounds is rather limited in contrast to the allylation. 2-Bromoallylation of aldehydes with 2,3-dibromopropene could be effectively achieved using Sn/HBr.[2a] Besides 2-bromoallyltin reagent 2-bromoallylboranes can also be used.[3]

Although allylindium reagent has received much attention in recent years,[6,7] an indium-mediated 2-bromoallylation of aldehydes has not been developed.[4] Many research groups examined the reaction; however, they failed completely or obtained the desired product in very low yield.[8] Li and co-workers used 2-chloro-3-bromopropene instead of 2,3-dibromopropene in their indium-mediated 2-chloroallylation.[4a] Loh et al. carried out an indium-mediated 2-bromocrotylation in saturated aqueous NH_4Cl solution in the presence of $La(OTf)_3$ under sonication.[4b]

During our studies on the indium-mediated allylations,[7] we also found that indium-mediated 2-bromoallylation of 4-chlorobenzaldehyde (**1a**) with 2,3-dibromopropene afforded the product **2a** in low yield (33%) in the presence of indium in aqueous DMF at room temperature (3 h). We hypothesized that the unfavorable results might be due to the decomposition of 2-bromoallylindium reagent to allene, as shown in Scheme 1. Zinc-mediated dehalogenation of 2,3-dihalopropene is a well-known method of allene.[9] The decomposition of 2-bromoallylindium reagent has also been observed by Minehan and co-workers in their attempted reaction of D-glyceraldehyde acetonide and 2,3-dibromopropene in aqueous DMF.[8a] Actually, when we ran the reaction in aqueous DMF at room temperature, we observed an exothermic reaction and gas evolution as Minehan and co-workers have reported. Thus, we examined the reaction of 4-chlorobenzaldehyde and 2,3-dibromopropene at low temperature (−20 °C). To our delight, the desired product **2a** was obtained in 71% yield in short time (3 h).[10] However, trace amounts of 4-chlorobenzaldehyde remained even though excess amounts of 2,3-dibromopropene (3.0 equiv) and indium (2.0 equiv) were employed. The results clearly state that 2-bromoallylindium reagent reacted with **1a** in part and destroyed in part, even at low temperature. Although we did not observe a gas evolution apparently at this



Scheme 1.

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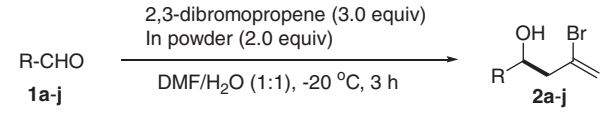
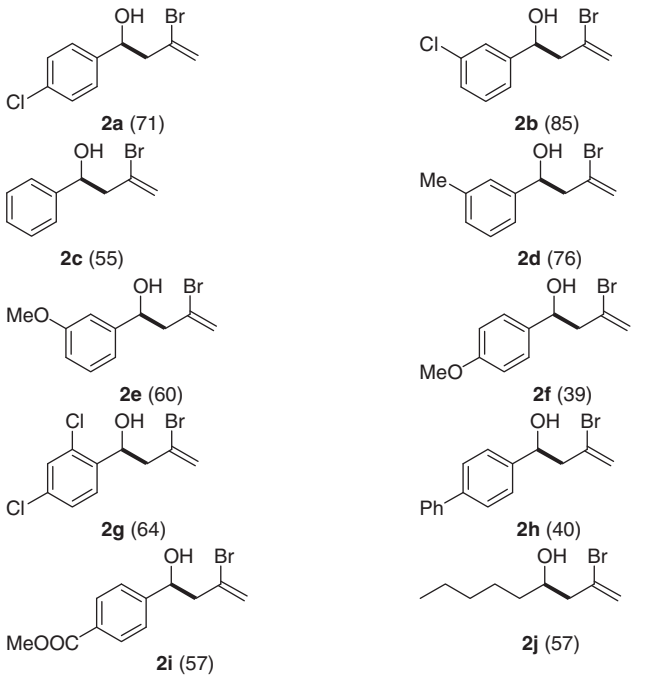
Table 1
In-mediated Barbier-type-2-bromoallylation of aldehydes[a]





[a] Isolated yield (%).

Table 2
Competetive decomposition and reaction of 2-bromoallylindium reagent[a]

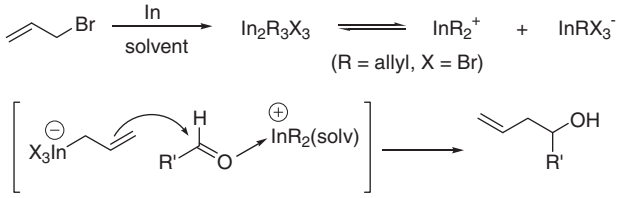
Entry	Conditions[b]	**2a**[c] (%)
1	(i) 2,3-Dibromopropene, indium, aqueous DMF, −20 °C, 3 h (ii) Then add **1a**, −20 °C (3 h), 20 °C (12 h)	<5
2	**1a**, 2,3-dibromopropene, indium, aqueous THF, −20 °C, 3 h	<5
3	(i) 2,3-Dibromopropene, indium, aqueous THF, −20 °C, 3 h (ii) Then add **1a**, 20 °C, 12 h	47
4	(i) 2,3-Dibromopropene, indium, aqueous THF, −20 °C, 3 h (ii) Then add **1a**, 20 °C, 12 h	18

[a] Compound **1a** was used as a model substrate.
[b] 2,3-Dibromopropene (3.0 equiv) and indium (2.0 equiv) were used.
[c] Isolated yield.

temperature, 2-bromoallylindium reagent must be destroyed slowly (vide infra).

Encouraged by the above results we examined an indium-mediated 2-bromoallylation of various aldehydes **1a**–**j**, and the results are summarized in Table 1. We used 2,3-dibromopropene (3.0 equiv) and indium (2.0 equiv) throughout all the entries although starting materials remained in appreciable amounts in some cases. As shown in Table 1, the yields of products (**2a**–**e**, **g**, **i**, and **j**) were moderate to good (55–85%). However, the yields of products (**2f** and **h**) were relatively low with *p*-anisaldehyde (**1f**) and *p*-phenylbenzaldehyde (**1h**). The reaction of 5-methylfurfural produced intractable complex mixtures and unfortunately we failed to isolate the desired product in an appreciable amount.

In order to get more insights we ran the reaction of **1a** under various conditions, and the results are summarized in Table 2. Firstly, we examined a decomposition of 2-bromoallylindium reagent in aqueous DMF at −20 °C. 2,3-Dibromopropene was added



Scheme 2.

to a mixture of indium in aqueous DMF at −20 °C and let the reaction mixture for 3 h at this temperature, and then **1a** was added and the reaction progress was monitored (entry 1). However, desired product **2a** was produced in trace amount (<5%) even after 15 h. The result stated that 2-bromoallylindium reagent was destroyed almost completely within 3 h at −20 °C in aqueous DMF. When we used aqueous THF instead of aqueous DMF as a reaction medium at −20 °C, **2a** was formed in trace amount (<5%), as shown in entry 2. The result stated that the reaction of 2-bromoallylindium reagent and **1a** was not effective in aqueous THF at −20 °C. But, decomposition of 2-bromoallylindium reagent at −20 °C was found to be negligible based on the experiment in entry 3. Actually, a moderate yield of **2a** (47%) was isolated at 20 °C when we added **1a** to a pre-generated 2-bromoallylindium reagent at −20 °C after 3 h. However, most of 2-bromoallylindium reagent was destroyed at 20 °C within 3 h even in aqueous THF, as can be seen in entry 4; however, decomposition rate of 2-bromoallylindium reagent is slower in aqueous THF than in aqueous DMF.

Very recently, Koszinowski reported a brilliant study on the heterolytic dissociation of allylindium reagent.[11] As shown in Scheme 2, an allylindium reagent $In_2R_3X_3$ undergoes heterolytic dissociation to yield ions such as InR_2^+ and $InRX_3^-$, and the extent of dissociation is greater in DMF than in THF. According to the report, the reactivity of allylindium reagent toward an aldehyde is great in DMF due to high concentration of nucleophilic allylindate anions, $InRX_3^-$. Based on the study of Koszinowski[11] and our own observations, the successful results of 2-bromoallylation in aqueous DMF could be understood as follows. 2-Bromoallylation of aldehyde is faster in aqueous DMF than in aqueous THF although a decomposition of 2-bromoallylindium reagent to allene is also faster in aqueous DMF.[12]

In summary, an indium-mediated 2-bromoallylation of aldehydes was carried out successfully to produce the corresponding 2-bromohomoallylic alcohols in moderate yields. The reaction was carried out at low temperature (−20 °C) in aqueous DMF in order to minimize the decomposition of 2-bromoallylindium reagent to allene.

Acknowledgments

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10. *Typical procedure for the synthesis of* **2a**: To a stirred mixture of **1a** (141 mg, 1.0 mmol) and indium (228 mg, 2.0 mmol) in aqueous DMF (1:1, 0.5 mL) was added dropwise a solution of 2,3-dibromopropene (Tech. 80%, 600 mg, 3.0 mmol) in aqueous DMF (1:1, 0.5 mL) during 5 min at −20 °C. The reaction mixture was stirred at −20 °C for 3 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O, 10:1) compound **2a** was obtained as colorless oil, 186 mg (71%). Other compounds were synthesised similarly, and some selected spectroscopic data of **2a**, **b**, **d**, **e**, **i**, and **j** are as follows.
Compound **2a**: 71%; colorless oil; IR (film) 3421, 1630, 1490, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (br s, 1H), 2.66–2.83 (m, 2H), 4.97–5.02 (m, 1H), 5.53 (d, J = 1.8 Hz, 1H), 5.65 (d, J = 1.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.25, 70.90, 120.33, 127.17, 128.62, 129.56, 133.45, 141.18; ESIMS m/z 243 (M^++H-H_2O), 245 (M^++H+2-H_2O), 247 (M^++H+4-H_2O). Anal. Calcd for $C_{10}H_{10}BrClO$: C, 45.92; H, 3.85. Found: C, 45.75; H, 3.91.
Compound **2b**: 85%; colorless oil; IR (film) 3424, 1630, 1431, 1275, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (d, J = 3.0 Hz, 1H), 2.66–2.82 (m, 2H), 4.95–5.00 (m, 1H), 5.53 (d, J = 1.8 Hz, 1H), 5.65 (d, J = 1.8 Hz, 1H), 7.18–7.29 (m, 3H), 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.16, 70.89, 120.35, 123.93, 125.94, 127.88, 129.47, 129.73, 134.35, 144.78; ESIMS m/z 243 (M^++H-H_2O), 245 (M^++H+2-H_2O), 247 (M^++H+4-H_2O). Anal. Calcd for $C_{10}H_{10}BrClO$: C, 45.92; H, 3.85. Found: C, 46.07; H, 3.79.
Compound **2d**: 76%; colorless oil; IR (film) 3420, 1631, 1275, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (d, J = 2.7 Hz, 1H), 2.34 (s, 3H), 2.67–2.84 (m, 2H), 4.93–4.98 (m, 1H), 5.51 (d, J = 1.5 Hz, 1H), 5.65 (d, J = 1.5 Hz, 1H), 7.06–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.37, 51.14, 71.48, 119.80, 122.80, 126.41, 128.34, 128.49, 130.14, 138.09, 142.76; ESIMS m/z 223 (M^++H-H_2O), 225 (M^++H+2-H_2O). Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.86; H, 5.15.
Compound **2e**: 60%; colorless oil; IR (film) 3450, 1630, 1601, 1488, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (br s, 1H), 2.70–2.86 (m, 2H), 3.81 (s, 3H), 4.98–5.02 (m, 1H), 5.53 (d, J = 1.8 Hz, 1H), 5.68 (d, J = 1.8 Hz, 1H), 6.80–6.84 (m, 1H), 6.94–6.96 (m, 2H), 7.24–7.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.20, 55.21, 71.46, 111.21, 113.29, 118.05, 119.99, 129.53, 130.03, 144.52, 159.70; ESIMS m/z 239 (M^++H-H_2O), 241 (M^++H+2-H_2O). Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10. Found: C, 51.71; H, 4.94.
Compound **2i**: 57%; colorless oil; IR (film) 3478, 1719, 1631, 1435, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.62 (br s, 1H), 2.70–2.86 (m, 2H), 3.90 (s, 3H), 5.06–5.10 (m, 1H), 5.53 (d, J = 1.8 Hz, 1H), 5.65 (d, J = 1.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.99 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.18, 52.09, 71.09, 120.31, 125.70, 129.41, 129.46, 129.74, 147.94, 166.86; ESIMS m/z 267 (M^++H-H_2O), 269 (M^++H+2-H_2O). Anal. Calcd for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.60. Found: C, 50.68; H, 4.49.
Compound **2j**: 57%; colorless oil; IR (film) 3417, 2928, 2857, 1629, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 6.6 Hz, 3H), 1.24–1.53 (m, 8H), 1.81 (br s, 1H), 2.46–2.60 (m, 2H), 3.87–4.00 (m, 1H), 5.54 (d, J = 1.5 Hz, 1H), 5.70 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.00, 22.56, 25.23, 31.72, 36.30, 49.35, 69.00, 119.52, 130.84; ESIMS m/z 203 (M^++H-H_2O), 205 (M^++H+2-H_2O). Anal. Calcd for $C_9H_{17}BrO$: C, 48.88; H, 7.75. Found: C, 49.13; H, 7.66.
11. Koszinowski, K. *J. Am. Chem. Soc.* **2010**, *132*, 6032–6040.
12. Based on the works of Koszinowski[11] and our own observations, we assumed that the reaction in aqueous THF at 20 °C could afford the product in a reasonable yield. Actually, the reaction of **1a** under the conditions (aqueous THF, 12 h, at 20 °C) gave 62% of **2a**. Similarly, the reaction of *p*-anisaldehyde afforded **2f** in 31% (aqueous THF, 14 h, at 20 °C).