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Reductive coupling reaction of aldehydes using indium(III) triflate as the catalyst

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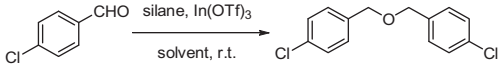
ABSTRACT

A reductive coupling reaction was effectively developed to convert an aldehyde to its symmetrical ether. The successful reactions required Et_3SiH and CH_2Cl_2 as the suitable solvent in the presence of a catalytic amount of $In(OTf)_3$. Various aldehydes were subjected to the method, and each afforded the expected ethers in good to excellent yields.

Ethers are a recognizable class of organic components in which two hydrocarbons are bound to both sides of one oxygen atom. Ether moieties are found in a couple of historically important natural products that made up early remedies in traditional natural medicines. Many studies in the fields of chemistry and pharmacology have included therapeutic natural products to date.[1] The most venerable examples of ether-containing natural products include morphine, digitoxin, paclitaxel, quinine, artemisinin, and halichondrin B. Morphine is an opium alkaloid that is used as a pain reliever, and digitoxin is a glycoside that exhibits cardiotonic activity. Paclitaxel is a widely used pharmaceutical agent under the name of Taxol for the treatment of breast cancer. Both quinine and artemisinin show anti-malarial activity, although the mechanism of action toward a cure is different. Halichondrin B was selected for further structural development as a cell proliferation inhibitor in the treatment of breast carcinoma. Synthetic chemistry was accomplished by Avery et al. for the total synthesis of artemisinin along with its analogues.[2,3] Also, halichondrin B was successfully synthesized and reported by Kishi et al. in 1992.[4]

The Williamson ether synthesis is the most fundamental method for the preparation of ethers, in which an alkoxide is reacted with an alkyl halide.[5] Since the introduction of the Williamson method, decades of intensive research have taken place with ether, and many modifications for homocoupling and heterocoupling have been introduced, including the reductive etherification of carbonyl compounds. Several reports utilized organosilicon reagents such as Et_3SiH, Me_3SiH, and $PhSiH_3$ in the presence of Lewis acid activators, including $BF_3{\cdot}Et_2O$,[6] TMSI,[7,8] TMSOTf,[9,10] $BiBr_3$,[11] $BiCl_3$,[12] $FeCl_3$,[13,14] $TrClO_4$,[15] and SbI_3.[16] Precedently, syntheses of symmetrical ethers by means of reductive etherification of aldehydes using 1,1,3,3-tetramethyldisiloxane (TMDS) and $Cu(OTf)_2$ have been reported with efficient results.[17]

Table 1
The search for the appropriate combination of silane reagents and solvents



Entry[a]	Silane	Solvent	Time	Yield[b] (%)
1	Et_3SiH	CH_3CN	24 h	N.R.
2	Et_3SiH	THF	24 h	N.R.
3	Et_3SiH	Toluene	48 h	N.R.
4	Et_3SiH	$CHCl_3$	24 h	60
5	Et_3SiH	CH_2Cl_2	24 h	90
6	$PhSiH_3$	CH_2Cl_2	24 h	N.R.
7	$PhMe_2SiH$	CH_2Cl_2	3 days	46

[a] For all reactions, 4 equiv of silane and 10 mol % of $In(OTf)_3$ were used.
[b] Isolated yields.

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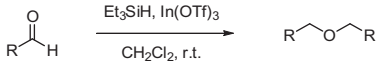
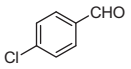
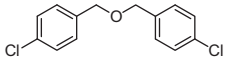
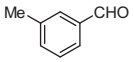
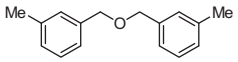
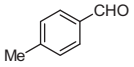
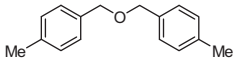
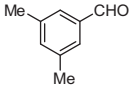
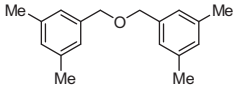
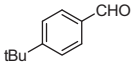
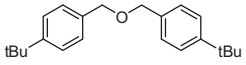
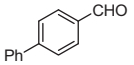
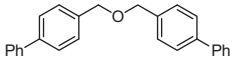
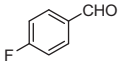
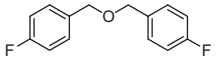
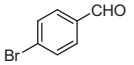
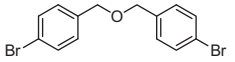
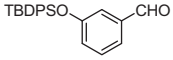
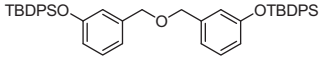
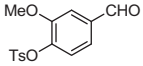
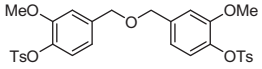
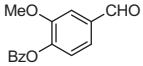
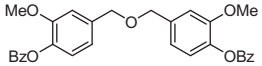
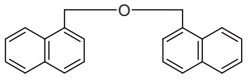
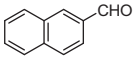
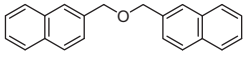
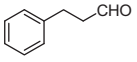
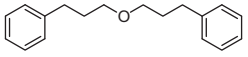
0040-4039/

Table 2
The reductive coupling reaction of aldehydes



Entry[a]	Substrate	Product	Time (h)	Yield[b] (%)
1			24	90
2			40	84
3			43	80
4			187	63
5			20	89
6			4	90
7			24	85
8			17	63
9			5	74
10			4	97
11			4	76
12			23	73
13			23	80
14			17	87

[a] For all reactions, 4 equiv of silane and 10 mol % of $In(OTf)_3$ were used.
[b] Isolated yields.

Other systems for the preparation of ethers using catalytic zinc reagents have also been demonstrated.[18,19] Consequently, a recent trend has extended the examination of etherification and applied Lewis acids of indium, such as $InCl_3$ and $InBr_3$.[20,21]

We have focused on the utility of an indium reagent, and several studies have reported the catalytic application of trivalent $In(OTf)_3$, as well as that of indium metal.[22–28] In our ongoing efforts to explore indium-utilized chemistry, we have found that the catalytic use of $In(OTf)_3$ could enhance the reductive coupling reaction of aldehydes, converting the initial aldehydes to their symmetrical ethers. Herein, we report the details of our study.

In the initial search for the appropriate combination of silane reagents and solvents, we attempted preliminary experiments using 4-chlorobenzaldehyde as the starting substrate. Based on the precedent examples, we considered Et_3SiH as our first choice, and several solvents were examined employing $In(OTf)_3$ as the catalyst (Table 1). The reactions using CH_3CN, THF, and toluene were terminated because there was no reaction, and the starting material of 4-chlorobenzaldehyde was recovered intact after 24 or 48 h (Table 1, entries 1–3). On the other hand, transformations using chlorinated solvents led to the desired symmetrical ethers (Table 1, entries 4 and 5).[19] In particular, CH_2Cl_2 was the most efficient solvent and gave an excellent yield of 90%. This high yield might be due to the suitable polarity of CH_2Cl_2, in which the ether products could remain stable. The use of other silane reagents was then investigated, keeping CH_2Cl_2 as the solvent. However, replacement with other silane reagents worsened the results (Table 1, entries 6 and 7).

With the successful conditions for a reductive coupling reaction in hand, various aldehydes were subjected to this method in order to pursue the scope and applicability. As shown in Table 2, many benzaldehyde derivatives were efficiently transformed to symmetrical ethers.[29–35] The 3- and 4-methyl substituted benzaldehyde derivatives furnished the products in high yields (Table 2, entries 2 and 3),[29] and 3,5-dimethyl benzaldehyde also gave a good yield, despite a longer reaction time (Table 2, entry 4). Furthermore, the aldehydes with other hydrocarbon and halogen substituents successfully afforded the corresponding ethers in good to excellent yields (Table 2, entries 5–8).[30–32] Since the free phenol moiety affected reaction course, the protection of phenol groups was thus

advanced. The *tert*-butyldiphenylsilyl (TBDPS) protecting group gave good results in maintaining the function of protection (Table 2, entry 9). Also, tosyl (Ts) and benzoyl (Bz) groups protected vanillin, a natural product found in vanilla beans, and the substrates were effectively transformed to the expected ethers (Table 2, entries 10 and 11). Etherification was then extended to bicyclic and aliphatic compounds under the same reaction processes. The 1- and 2-naphthaldehydes gave the corresponding ethers in sufficient yields (Table 2, entries 12 and 13),[33] and the reaction of 3-phenylpropanal also resulted in a high yield of its symmetrical ether (Table 2, entry 14).[17,34] Compared with precedent report using TMDS and $Cu(OTf)_2$ to prepare symmetrical ethers,[17] we extended the array of benzaldehyde derivatives and bicyclic aromatics, and validated the method with Et_3SiH and $In(OTf)_3$. Furthermore, protecting groups attempted were not cleaved by these reaction conditions.

In summary, by employing $In(OTf)_3$ as a catalyst, a reductive coupling reaction was effectively developed that converts an aldehyde to its symmetrical ether. Various aldehydes were subjected to this method, and each afforded the expected ethers in good to excellent yields. A tolerance of protecting groups such as TBDPS, Ts, and Bz was also revealed. Further study of the application of this method is ongoing.

General experimental procedure: The typical experimental procedure included a starting material of 4-chlorobenzaldehyde (141 mg, 1 mmol) dissolved in dehydrated CH_2Cl_2 (10 mL) in a 100 mL flask equipped with a magnetic stirrer. Subsequently, $In(OTf)_3$ (56 mg, 10 mol %) was added at room temperature. Et_3SiH (0.64 mL, 4 mmol) was added via a syringe, and the reaction mixture was stirred under argon at room temperature for 24 h. The reaction completion was monitored by TLC, and the reaction mixture was condensed using a rotary evaporator. Flash column chromatography on silica gel furnished the desired ether product, which was confirmed by spectroscopy.

Acknowledgment

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35. Experimental data for Table 2.
Bis(3-methyl)benzyl ether (Table 2, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, 2H, J = 7.5 Hz), 7.18–7.14 (m, 4H), 7.01 (d, 2H, J = 7.5 Hz), 4.51 (s, 4H), 2.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 138.0, 128.5, 128.3, 128.2, 124.8, 72.1, 21.3; FT-IR (NaCl): 3026.41, 2920.32, 2856.67, 1610.61, 1489.10, 1456.30, 1354.07, 1159.26, 1082.10, 777.34, 694.40 cm^{-1}; MS (ESI$^+$) m/z [M+H]$^+$ calcd for $C_{16}H_{18}O$, 227; found, 227.
Bis(3,5-dimethyl)benzyl ether (Table 2, entry 4): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 4H), 6.98 (s, 2H), 4.54 (s, 4H), 2.37 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 137.9, 129.2, 125.7, 72.2, 21.2; HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for $C_{18}H_{22}O$, 277.1563; found, 277.1586.
Bis(4-phenyl)benzyl ether (Table 2, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62–7.60 (m, 8H), 7.48–7.43 (m, 8H), 7.36 (t, 2H, J = 7.5 Hz), 4.65 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.9, 140.6, 137.3, 128.8, 128.3, 127.3, 127.2, 127.1, 71.9; HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for $C_{26}H_{22}O$, 373.1563; found, 373.1593.
Bis(3-tert-butyldiphenylsilyloxy)benzyl ether (Table 2, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 8H, J = 8.0 Hz), 7.54–7.47 (m, 12H), 7.16 (t, 2H, J = 8.0 Hz), 6.97–6.93 (m, 4H), 6.83 (d, 2H, J = 8.5 Hz), 4.39 (s, 4H), 1.29 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 139.6, 135.5, 132.8, 129.8, 129.1, 127.7, 120.4, 119.1, 118.8, 71.4, 26.5, 19.4; HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for $C_{46}H_{50}O_3Si_2$, 729.3191; found, 729.3206.
Bis(3-methoxy-4-tosylhydroxy)benzyl Ether (Table 2, entry 10): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 4H, J = 8.0 Hz), 7.30 (d, 4H, J = 8.0 Hz), 7.10 (d, 2H, J = 8.0 Hz), 6.86–6.83 (m, 4H), 4.49 (s, 4H), 3.57 (s, 6H), 2.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.6, 145.0, 138.1, 137.5, 132.9, 129.2, 128.4, 123.6, 119.4, 111.6, 71.6, 55.4, 21.5; HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for $C_{30}H_{30}O_9S_2$, 621.1223; found, 621.1246.
Bis(4-benzoyloxy-3-methoxy)benzyl ether (Table 2, entry 11): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, 4H, J = 8.0 Hz), 7.64 (t, 2H, J = 7.5 Hz), 7.52 (t, 4H, J = 8.0 Hz), 7.17 (d, 2H, J = 8.0 Hz), 7.09 (d, 2H, J = 2.0 Hz), 7.01 (dd, 2H, J = 8.0, 1.5 Hz), 4.62 (s, 4H), 3.84 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 151.3, 139.3, 137.1, 133.4, 130.2, 129.3, 128.4, 122.7, 119.8, 111.7, 71.7, 55.8; HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for $C_{30}H_{26}O_7$, 521.1571; found, 521.1575.
Bis(2-naphthyl)methyl ether (Table 2, entry 13): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88–7.85 (m, 8H), 7.54 (dd, 2H, J = 8.5, 1.5 Hz), 7.52–7.47 (m, 4H), 4.78 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 133.3, 133.0, 128.2, 127.9, 127.7, 126.6, 126.1, 125.9, 125.8, 72.2; HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for $C_{22}H_{18}O$, 321.1250; found, 321.1253.