A simple and inexpensive procedure for low valent copper mediated benzylation of aldehydes in wet medium

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Abstract
An operationally simple, inexpensive and efficient procedure for benzylation of aldehydes in wet medium has been developed that was mediated with low valent copper, prepared *in situ* through spontaneous reduction of $CuCl_2$-$2H_2O$ with magnesium *in situ*. Notably, copper mediated benzylation of **3h** took place with good *syn* selectivity that was opposite to that for the corresponding Grignard addition. Finally, homobenzyl alcohol **5a** was elegantly transformed into a known protease inhibitor synthon **I**.

Keywords: benzylation, wet medium, bimetal redox strategy, *syn*-selectivity, (*R*)-2,3-cyclohexylideneglyceraldehyde, α-chelate cyclic model, protease inhibitor synthon

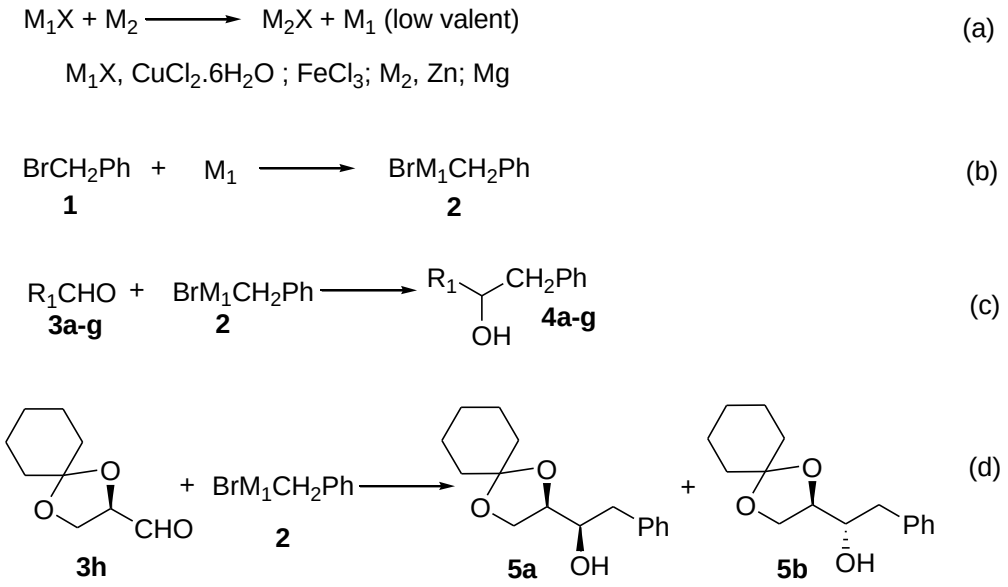
Introduction

Carbon-carbon bond formation is the essence of organic synthesis. In this regard, metal mediated carbon-carbon bond forming reactions is always treated as a useful strategy in organic synthesis. Consequently, over the ages exploration of the potentials of various metals to promote various types of Barbier type addition of organic halides to electrophiles has become a topic of wide attention.[1] It is well known that to mediate any C-C bond forming reaction, obtaining a metal in suitably active form under the reaction condition is of high importance. Furthermore, apart from its nature, the method of its activation plays a good role in directing the stereo-selectivity in the case of asymmetric additions. In this perspective, there is a scope for studying the potential of different metals in their various active forms to promote Barbier type additions to carbonyls.

Benzylation of aldehydes is an important type of Barbier type carbon-carbon bond forming reactions in organic synthesis. The homobenzylic alcohols produced from such reactions due to their functional richness are amenable for versatile applications in organic synthesis.[2] A very common procedure traditionally practiced to prepare homobenzylic alcohols is *via* Grignard addition of benzylic bromides to carbonyls which can only be performed in anhydrous reaction

media. In addition, some other strategies were reported in earlier days to prepare homobenzylic alcohols involving hydroboration of 1-aryl-alkenes,[3] solvolyses of sulfonates obtained from aromatic bridged hydrocarbons[4] and regio-selective hydrogenation of aromatic epoxides in recent years[5] etc. Recently, in view of current attention on performing many organic reactions in environmentally friendly aqueous media,[6] considerable attention has been focused on performing Barbier type additions of benzyl bromide to aldehydes mediated with metals *viz* Cd obtained from tri-metal system,[7a] Zn in presence of Ag catalyst,[7b] etc. In a recently reported approach, silver catalysed Mn mediated Barbier type benzylation can be performed in highly anhydrous THF.[8]

We present here a very simple and practically viable procedure for benzylation of aldehydes in wet solvent. Our strategy was based on judicious application of bimetal redox strategy (Scheme 1) [9] to effect this reaction in wet condition.[9] Earlier, this approach was applied to perform two C-C bond forming reactions successfully *viz* allylation [9a,b] and Reformatsky reaction[9c] in distilled THF. Interestingly, to carry out the afore-mentioned allylation and Reformatsky reaction through application of bimetal redox strategy, the low valent metal mediators needed to be prepared *in situ* by reduction of their salts with different reducing metals *viz* Zn[9a,b] and Mg[9c] respectively. From these two instances, it could be suggested that the choice of a suitable combination of reducing metal and reducible salt is of high importance regarding the efficacy of a C-C bond forming reaction in moist condition according to this bimetal redox strategy (Scheme 1). However, all the above mentioned C-C bond forming reactions[9a-c] could be performed efficiently in distilled THF whose inherent moisture content[10] distinctly favored such organometallation (as shown in Scheme 1).



Scheme 1. Low valent metal mediated benzylation of aldehydes.

We once again attempted to explore the scope of this strategy for benzylation of aldehydes in distilled THF. Based on our earlier success,[9a-c] we decided to investigate on the efficacy of the present reaction using all four possible combinations between two reducible salts (M_1X), *viz* $FeCl_3$ (97%, Aldrich) and $CuCl_2$-$2H_2O$ (Aldrich) and two reducing metals (M_2) *viz* Zn dust (SRL India) and magnesium turning (SRL India). Three classes of aldehyde substrates were chosen, viz aliphatic (**3a-c,** Aldrich), aromatic (**3d-g**, Aldrich) and a chiral **3h**[11] with a view to exploring the generality of this strategy. (Scheme 1) In all these heterogeneous reactions, an aldehyde was treated with excess amounts of reagents *viz* benzyl bromide (Aldrich), salt M_1X and reducing metal M_2 to ensure their smooth progress.

Table-1. Low valent Cu mediated Benzylation reaction of aldehydes

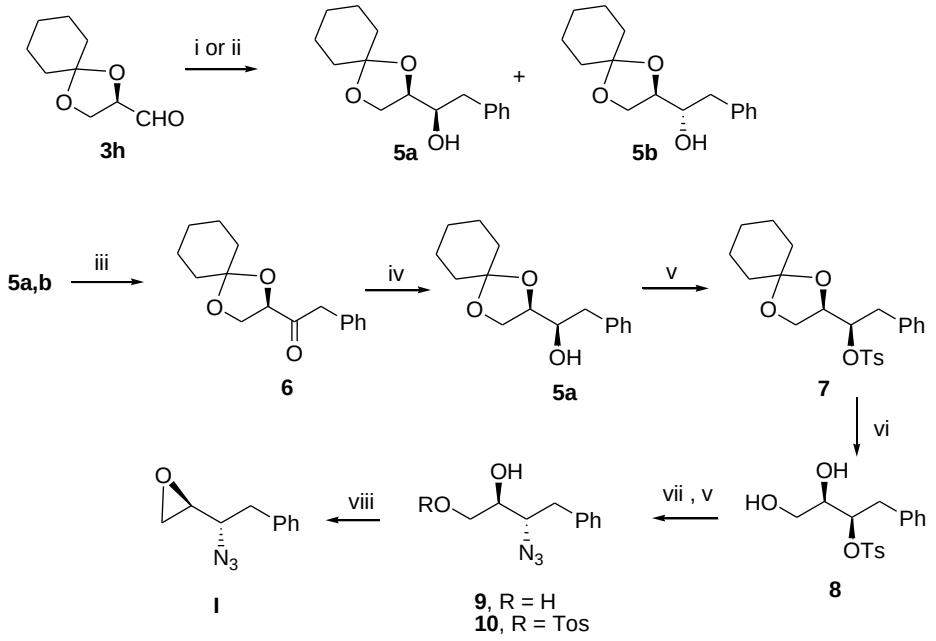
Entry	R_1 of Aldehyde	Aldehyde: Mg):$CuCl_2$, $2H_2O$: $PhCH_2Br$	Time hr	product	% yield	Product ratio
a	*n*-C_6H_{13} **3a**	1.0: 4.0:4.0:1.5	18	**4a**[a]	61.8	
b	*n*-C_9H_{19} **3b**	1.0: 4.0:4.0:1.5	16	**4b**[b]	64.4	
c	*n*-$C_{13}H_{27}$ **3c**	1.0: 4.0:4.0:1.5	16	**4c**	57.8	
d	C_6H_5 **3d**	1.0: 3.0:3.0:1.5	9	**4d**[a]	71.7	
e	3-$MeOC_6H_5$ **3e**	1.0: 3.0:3.5:1.5	8	**4e**	73.8	
f	4-Et-C_6H_5 **3f**	1.0: 3.0:3.5:1.5	7	**4f**	70.7	
g	4-Cl-C_6H_5 **3g**	1.0: 4.0: 4.0:1.5	11	**4g**[a]	68.9	
h	(*R*)-2,3-cyclohexylideneglyceral **3h**	1.0: 7.0:7.0:2.5	20	**5a & 5b**	68.4	**5a** : **5b** :: 80: 20[c]

[a] The compounds were characterized from their spectral data (reference 7b)
[b] the compound was characterized from its spectral data (reference 12)
[c] The ratio was determined from ^{13}C NMR of the product (reference 13)

Results and Discussion

Using zinc as reducing metal in combination with either of the metal salts (Zn/ $CuCl_2$-$2H_2O$ or Zn/$FeCl_3$), was found to be ineffective for reactions with all the aldehydes **3a-h.** Likewise, using the combination of Mg/ $FeCl_3$ also did not give any encouraging sign of progress with any of these aldehydes. However, to our great delight the combination of Mg / $CuCl_2$, $2H_2O$ was found to be highly favorable for benzylation of all the aldehydes producing corresponding homobenzylic alcohols in good yields. (Table 1 and Scheme 1, **4a-g** from **3a-g**, **5** from **3h**). Among the successful reactions, aromatic aldehydes reacted more efficiently at comparatively faster rates (entries d-g, Table 1) with respect to aliphatic ones. Benzylation with **3h** (entry h,

Table 1) took place to produce homobenzylic alcohol **5** in reasonably good yield (68.4%) and *syn* selectivity (*syn*-**5a** : *anti*-**5b** 80 : 20). Owing to the inseparability of the diastereomers **5a**/**5b** by column chromatography, their ratio could be assayed from ^{13}C NMR spectrum[13] of this mixture. The predominant formation of *syn*-**5a** for (entries s, Table 1) gave evidence of the fact that all the reactions took place *via* the addition of the corresponding organocopper reagents **2** (Scheme 1) through α-chelate cyclic model.[14] It is worth mentioning that the corresponding benzyl-Grignard addition to **5a** took place with lower yield (43.8 %) compared to the organo-copper addition done above and with *anti* selectivity (*syn*-**5a** : *anti*-**5b** : 35 : 65, vide ^{13}-C NMR *supporting information*)[13].



i) $PhCH_2MgBr$, THF, rt; ii) Mg / $CuCl_2$, $2H_2O$, THF iii) PCC, CH_2Cl_2; iv) K-selectride, -78^{o}C, THF; v) TosCl, Py, 0^{o}C; vi) Aq CF_3COOH, 0^{o}C; vii) NaN_3, DMF, heat; viii) K_2CO_3, MeOH.

Scheme 2. Synthesis of target molecule I.

The proportion of *syn*-**5a** in this distereoisomeric mixture has been increased (Scheme 2) following a known oxidation-reduction protocol.[15] Thus, PCC oxidation of the diastereoismeric mixture **5a**,**b** to afford ketone **6** which on reduction with K-selectride yielded *syn*-**5a** with 99% stereo-selectivity.[13] Tosylation of **5a**, followed by deketalization of the resulting tosylate **7** in acidic condition afforded crude diol **8** which on treatment with NaN_3 afforded **9**[16b,d,e, 17] in good yield. Monotosylation of the primary hydroxyl of **9** and base treatment of the resulting tosylate **10** yielded azido epoxide **I**, a key synthon[16] of a HIV protease inhibitor. (Scheme 2) Our synthesized compound **I** were characterized from the conformity of its physical, spectral and optical data with the reported ones.[16]

Thus, a very mild and efficient procedure for benzylation of aldehydes has been developed. The novelty of the approach was due to smooth exploitation of the spontaneous bimetal redox reaction in an environmentally benign wet condition between commercially available chemicals, Mg and $CuCl_2$, $6H_2O$ in THF to effect this important carbon-carbon bond formation. The inexpensiveness, practical viability and good yields with varied types of aldehyde substrates (**3a-h**, Table 1) associated with this non hazardous procedure are of immense significance regarding its overall efficacy. Finally, as a representative application of the this work, benzylation product of **3h** has been judiciously exploited in a simple and straight forward manner (Scheme 2) to prepare a key synthon **I**[16] of a protease inhibitor.

Experimental Section

General. Chemicals used as starting materials are commercially available and were used without further purification. All solvents used for chromatography and extraction were distilled twice at atmospheric pressure prior to use. Moist THF was distilled once prior to use in all bimetal redox reactions. For anhydrous reactions, THF was dried by heating over $LiAlH_4$. IR spectra were recorded with a Perkin-Elmer 837 spectrophotometer. ^1H and ^{13}C NMR spectra were scanned with a Bruker Ac-200 (200 MHz) instrument in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS Optical rotations were measured with a JASCO DIP-360 polarimeter; $[\alpha]_D$ values are given in units of 10^{-1}deg cm^{-3} g^{-1} .

General procedure of low valent metal mediated benzylation reaction

To a well stirred mixture of aldehyde **3** (0.01mol), benzyl bromide **2** (2.57 g, 0.015 mol for **3a-h** and 4.28g for **3i**) and $CuCl_2$-$2H_2O$ (6.8 g, 0.04 mol for **3a-c, g**; 5.1 g, 0.03mol for **3d**; 5.95, 0.035mol for **3e, f** ; 11.9 g, 0.07mol for **3h**) or $FeCl_3$ (6.48 g, 0.04 mol for **3a-c, g**; 4.86 g, 0.03mol for **3d**; 5.66, 0.035mol for **3e,f** ; 8.1 g, 0.05mol for **3h**) in THF (100 mL) was added Mg turnings (960 mg, 0.04 mol for **3a-c, g**; 720 mg, 0.03mol for **3d-f**; 1.68 g, 0.07mol for **3h**) or Zn dust (2.6 g, 0.04 mol for **3a-c, g**; 1.95 g, 0.03mol for **3d-f**; 3.25 g, 0.05mol for **3h**) in one lot. The mixture was stirred at the ambient temperature for the period as shown in Table. No reaction was found to take place in the cases with Zn/$CuCl_2$, $2H_2O$ or Zn/$FeCl_3$ or Mg/ $FeCl_3$ (*vide* TLC). For reactions with Mg/ $CuCl_2$, $2H_2O$, benzylation product was produced for all cases (*vide* TLC). The reaction mixture was then treated successively with water (50 mL) and EtOAc (100 mL), stirred for 10 min more and then filtered. The filtrate was treated with 2% aqueous HCl to dissolve a little amount of suspended particles. The organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water, brine and then dried. Solvent removal and column chromatography of the residue (silica gel, 0-20 % EtOAc in petroleum ether) afforded the desired benzylation products in pure form.

1-Phenylpentadecan-2-ol (4c). ^1H NMR ($CDCl_3$): δ 0.97 (bt, 3H), 1.2-1.6 (m, 24H), 1.7 (bs, 1H), 2.73 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.93 (dd, *J* = 13.6 , 4.4 Hz, 1H), 3.8-3.9 (m, 1H), 7.2-7.5

(m, 5H). ^{13}C NMR ($CDCl_3$): 14.1, 22.6, 25.7, 29.3, 29.6, 31.9, 36.8, 44.0, 72.6, 126.4, 128.5, 129.4, 138.6. Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.91. Found: C, 82.64; H, 12.14.

1-(3-Methoxyphenyl)-2-phenylethanol (4e). ^{1}H NMR ($CDCl_3$): δ 1.98 (bs, 1H), 3.10 (m, 2H), 3.8 (s, 3H), 4.97 (dd, *J*= 8.0, 5.2 Hz, 1H), 6.9-7.2 (m, 3H), 7.3-7.4 (m, 6H). ^{13}C NMR ($CDCl_3$): 45.5, 54.8, 74.8, 111.0, 112.8, 118.0, 126.1, 128.0, 129.0, 129.2, 137.8, 145.3, 159.2.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.98; H, 6.80.

1-(4-Ethylphenyl)-2-phenylethanol (4f). ^{1}H NMR ($CDCl_3$): δ 1.43 (t, *J* = 7.6 Hz, 3H), 2.26 (s, 1H), 2.84 (q, *J*= 7.8 Hz, 2H), 3.16 (m, 2H), 5.0 (m, 1H), 7.3-7.5 (m, 9H). ^{13}C NMR ($CDCl_3$): 15.5, 28.4, 45.8, 75.0, 125.8, 126.4, 127.7, 128.3, 129.4, 138.2, 141.0, 143.5.

Addition of benzyl Grignard to 3h

A solution of benzyl bromide (3.42 g, 0.02 mole) in Et_2O (50 mL) was added drop wise over a period of 2h to a stirred suspension of Mg (600 mg, 0.025 mole) in (50 mL) at room temperature. The mixture was stirred for 3h more at room temperature to produce benzylGrignard and cooled to -40 ºC. To it, a solution of **3h** (1.70g, 0.01mol) in Et_2O (50 mL) was added over a period of 1 h. The mixture was stirred for 2h at -40^0 C, gradually brought to room temperature and stirred for 3 h more. Saturated aqueous NH_4Cl (10 mL) was added to it. The mixture was extracted with EtOAc. The combined organic extract was washed with water, brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-20 % EtOAc in petroleum ether) afforded the pure **5** (1.15 g, 43.8%) containing an inseparable mixture of diastereomers (**5a,b**) (*syn* **5a**: *anti* **5b** : 35:65, as determined from ^{13}-C-NMR (*supporting information*) of the mixture (reference 13)).

(3*R*)-3,4-*O*-Cyclohexylidene-2-oxo-1-phenylbutane-3,4-diol (6). To a stirred suspension of pyridinium chlorochromate (2.6 g, 0.012 mol) in CH_2Cl_2 (60 mL) was added a solution of **5a, 5b** (2.1 g, 0.008mol). The mixture was stirred at ambient temperature for nearly 3 h till the disappearance of the starting material (TLC), diluted with diethyl ether (50 mL) and filtered through a column of celite. Solvent removal of the filtrate under reduced pressure and colum chromatography of the residue (silica gel, 0-15% EtOAc-petroleum ether) afforded pure **6** (1.56 g, 74.3%). $[\alpha]_D^{26}$ 10.40 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.2-1.6 (m, 10H), 3.7-4.3 (m, 4H), 4.4-4.5 (m, 1H), 7.1-7.3 (m, 5H). ^{13}C NMR ($CDCl_3$): 23.6, 23.9, 24.9, 34.3, 35.6, 45.3, 66.0, 79.4, 111.6, 126.8, 128.4, 129.6, 133.2, 207.9. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74. Found: C, 73.99; H, 7.55.

(2*R*,3*R*)-3,4-*O*-Cyclohexylidene-1-phenylbutane-2,3,4-triol (5a). Following the procedure reported earlier,[15] a solution of **6** (1.4 g, 5.38 mmol) in THF (30 mL) was reduced with K-selectride (5.5 mL of 1 molar in THF, 5.5 mmol) at -78 ºC**.** Similar work up and column chromatography (silica gel, 0-20 % EtOAc-petroleum ether) of the crude product afforded **5a** (1.32 g, 93.6%). $[\alpha]_D^{25}$ 9.12 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.2-1.6 (m, 10H), 2.40 (bs, 1H), 2.7-2.8 (m, 2H), 3.64-3.78 (m, 2H), 3.87-4.0 (m, 2H), 7.2-7.3 (m, 5H). ^{13}C NMR ($CDCl_3$): 23.6, 23.9, 25.0, 34.6, 36.1, 40.1, 65.5, 72.9, 77.4, 109.7, 126.3, 128.3, 129.2, 137.6 Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.38; H, 8.62.

(2*R*, 3*R*)- 3,4-*O*-Cyclohexylidene-2-*O*-*p*-toluenesulphonyl-1-phenyl-butane-2,3,4-triol (7). To a cooled (0 ºC) solution of **5a** (786 mg, 3 mmol) in Pyridine (4 mL) containing DMAP (50 mg) was slowly added a *p*-toluenesulfonylchloride (575 mg, 3 mmol). The mixture was stirred at 0 ºC for 6 h. After the reaction was complete (monitored with TLC), it was quenched by addition was water and extracted with $CHCl_3$. The organic layer was washed successively with 5% aqueous HCl, water, brine and then dried. Solvent removal under reduced pressure, and column chromatography of the residue (silica gel, 0-20 % EtOAc-petroleum ether) afforded **7** (1.14 g, 91.1%).$[\alpha]_D^{25}$ 32.8 (c 3.2, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 1.4-1.6 (m, 10H), 2.39 (s, 3H), 2.78 (q, *J* = 7.2 Hz, 1H), 3.10 (dd, *J* = 13.8, 6.4 Hz, 1H), 3.7-3.9 (m, 2H), 4.2 (m, 1H), 4.6 (m, 1H), 7.04-7.25 (m, 7H), 7.58 (d, *J*= 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.3, 23.5, 23.6, 24.9, 34.2, 35.4, 36.5, 64.4, 74.1, 82.1, 110.0, 126.4, 127.4, 128.2, 129.3, 129.4, 133.3, 135.5, 144.2. Anal. Calcd for $C_{23}H_{28}O_5S$: C, 66.32; H, 6.72; S,7.69. Found: C, 66.14; H, 6.65; S,7.89.

(2*S*, 3*R*)- 2-Azido -1-phenyl-butane-3,4-diol (9). To a cooled (0 ºC) solution of **7** (832 mg, 2 mmol) in CH_2Cl_2 (40 mL) was added 90% aqueous CF_3COOH solution (5 mL). The mixture was stirred for 4h till the total disappearance of starting material (TLC), diluted with water (100 mL) and extracted with $CHCl_3$. the combined organic extract was washed thoroughly with water and brine. Solvent removal under reduced pressure afforded the crude residue of **8** which was taken in DMF (30 mL). The solution was treated with NaN_3 (163 mg, 2.5 mmol) and heated (80 ºC) along with stirring for 4h. Most of DMF in the mixture was distilled off under reduced pressure and the residue was taken in water, extracted with EtOAc. The combined organic extract was washed successively with water, brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-15 % EtOAc-petroleum ether) afforded **9** (308 mg, 74.1 %) as a white solid. Mp 80-81ºC, lit[16e] mp 80-82ºC; $[\alpha]_D^{25}$ 30.2 (c 1.8, $CHCl_3$); lit[16b]$[\alpha]_D^{25}$ 30.6 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.26 (bs, 2H), 2.72-2.83 (m, 1H), 2.92-3.09 (m, 1H), 3.6-3.8 (m,4H), 7.29 (m, 5H). ^{13}C NMR ($CDCl_3$): 36.9, 63.1, 65.5, 73.0, 126.9, 128.6, 129.2, 137.2.

2*S*-[1(S)-Azido-2-phenylethyl]oxirane (I). To a cooled (0 ºC) solution of **9** (207 mg, 1 mmol) in pyridine (4 mL) was slowly added *p*-toluenesulfonylchloride (200mg, 1.05 mmol). The mixture was stirred overnight at 0 ºC. After the reaction was complete (monitored with TLC), it was quenched by addition was water and extracted with $CHCl_3$. The organic layer was washed successively with 5% aqueous HCl, water, brine and then dried. Solvent removal under reduced pressure afforded the residue containing **10** which was taken in MeOH (30 mL). The solution was mixed with K_2CO_3 (500 mg, 3.6 mmol) and stirred for 4h at room temperature. Excess MeOH was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed successively with water, brine and then dried. Solvent removal under reduced pressure and colum chromatography of the residue (silica gel, 0-10 % EtOAc-petroleum ether) afforded **I** (145 mg, 77.1%). $[\alpha]_D^{26}$ 12.9 (c 1.0, $CHCl_3$); lit[16d]$[\alpha]_D^{25}$ 12.9 (c 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.84-2.96 (m, 3H), 3.05 (d, *J* = 4.6 Hz, 1H), 3.11-3.17 (m, 1H), 3.64-3.71 (m, 1H), 7.33-7.47 (m, 5H). ^{13}C NMR ($CDCl_3$): 38.2, 45.1, 53.0, 63.5, 126.9, 128.5, 129.3, 136.5.

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10. Distilled THF always contains some amount of moisture. This provides partial (hydrated Cu and Co salts) and good ($FeCl_3$) solubility of the metal salts in it and facilitates bimetal redox reactions as well as subsequent C-C bond forming reactions (Scheme 1). It has been observed that in anhydrous THF none of the earlier reactions[9a-c] took place apparently due to very poor solubility of these metal salts.
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13. In general, *syn*-**5a** could be identified from its ^{13}C signals of the mixture of **5a** and **5b** at all regions appearing consistently at more downfield compared to the corresponding signals of *anti*-**5b**. This could be evident from the fact that following oxidation of this isomeric mixture and K-selectride reduction of **6** (ref 15), the downfield signals of *syn*-**5a** enhanced very much. Hence, by determining the ratio of ^{13}C signals of **5a,b**, their relative proportion in a diasterisomeric mixture could be estimated. This could be evident from the ^{13}C-NMR spectra

of **5a,b** mixtures obtained after low valent Cu mediated benzylation, benzyl Grignard addition and K-selectride reduction that was shown in the *Supporting Information*.

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