drous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate-hexane, 1 : 2, v/v) to afford N-methyl amide of (R)-N-(tert-butoxycarbonyl)-4-methoxyphenylglycine (2.63 g, 82.0%) as a white crystalline solid. mp 164-165 °C. ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.80 (d, 3H), 3.80 (s, 3H), 5.04 (d, 1H), 5.64-5.70 (m, 1H), 5.75-5.79 (m, 1H), 6.86 (d, 2H), 7.28 (d, 2H). IR (KBr) cm^{-1} 3306, 2976, 1700, 1657, 1513. $[\alpha]^{19.1}_D$ − 10.6 (c 0.1 CH_3OH).

N-Methyl amide of (R)-N-(tert-butoxycarbonyl)-4-methoxyphenylglycine (1.28 g, 4.35 mmole) was dissolved in 30 mL of THF. Trifluoroacetic acid (30 mL) was added to the stirred solution and then the mixture was stirred for 3 hrs. The reaction mixture was concentrated. The residue was dissolved in 50 mL of ethyl acetate and then washed with saturated K_2CO_3 solution. The organic solution was dried over anhydrous Na_2SO_4. To the stirred organic solution was added triethylamine (0.81 mL, 4.43 mmole) and acetyl chloride (0.31 mL, 4.43 mmole). The whole mixture was stirred for 5 min., washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate-hexane, 1 : 2, v/v) to afford N-methyl amide of (R)-N-acetyl-4-methyloxyphenylglycine, (R)-**2**, (0.91 g, 88.7%) as a light yellow crystalline solid. The enantiomeric purity of (R)-**2** was greater than 98% ee by HPLC analysis on a commercial chiral column derived from (S)-N-(3,5-dinitrobenzoyl)leucine.[5] mp 225-256 °C. ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.78 (d, 3H), 3.78 (s, 3H), 5.44 (d, 1H), 6.07-6.10 (m, 1H), 6.85 (d, 2H), 6.95 (d, 1H), 7.30 (d, 2H). IR (KBr) cm $^{-1}$ 3288, 3097, 2942, 1685, 1637, 1515. $[\alpha]^{21.8}_D$ − 172.8° (c 0.1, CH_3OH).

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Synthesis of a Polyhydroxylated Pyrrolidine by Regioselective Epoxide Ring-Openning

Sang Gyeong Lee* and Hyung Jae Jeong

Department of Chemistry and Research Institute of Natural Science, Gyeongsang National University, Chinju 660-701, Korea
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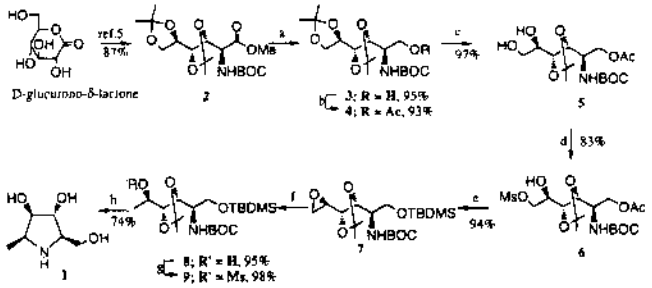
There is growing interest in synthetic methodologies towards polyhydroxylated piperidines and pyrrolidines since these compounds have been shown to possess potent inhibitory activities against various glycosidases.[1] These aza sugars have potential therapeutic utility in the treatment of various diseases, such as diabetes,[2] cancer,[3] and viral[4] infections. In view of interest in the structure and enzyme-inhibitory activity relationship, the demand for chemical modification of these compounds has increased. For this reason, many synthetic routes to natural or unnatural aza sugars have been developed over the last few years.

In connection with our project for the preparation of natural or unnatural aza sugars by new methods, here we describe a short and facile synthetic sequence for the synthesis of optically pure polyhydroxylated pyrrolidine **1** by regio- and stereoselective ring-openning of epoxide **7**. Pyrrolidine derivative **1** has methyl instead of hydroxy methyl group on the pyrrolidine ring and these analogs are still a somewhat unexplored class of aza sugars in spite of their interesting glycosidase inhibitory activity. Only one synthesis of isomers of **1** has been so far reported, which was attained *via* thermodynamic process of FDP aldolase catalyzed reaction with an α-substituted β-hydroxyaldehyde.[5]

The mannoate **2**[6] obtained in 87% yield from commercial

D-glucurono-δ-lactone, was smoothly reduced with $LiAlH_4$ in THF at rt to give the corresponding alcohol **3**. Subsequent protection of **3** with acetic anhydride in pyridine at rt produced **4** in 93% yield (Scheme 1). Selective cleavage

Scheme 1



Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C. (b) Ac_2O, py, rt. (c) Dowex 50W-X8, 90% MeOH. (d) MsCl, Et_3N, CH_2Cl_2, −10 °C. (e) (1) NaOH, MeOH, rt. (2) TBDMSCl, imidazole, DMF, rt. (f) $NaBH_3CN$ (10 eq), THF, reflux. (g) MsCl, Et_3N, CH_2Cl_2, −10 °C. (h) (1) Dowex 50W-X8, 90% MeOH. (2) Et_3N, MeOH, reflux.

of the terminal acetonide group in diacetal **4** proceeded with Dowex 50W-X8 resin (H^+ form) in 90% MeOH to generate **5** in 97% yield.[7] The primary hydroxy group of diol **5** was selectively mesylated with mesyl chloride in the presence of Et_3N in CH_2Cl_2 at −10 °C to furnish monomesylated alcohol **6** in 83% yield. Subsequent epoxidation of the resultant mesylate **6** with NaOH provided the strategic chiral epoxide **7** in 94% yield. By using this epoxide, we investigated the regio- and streoselective reductive opening of the epoxide **7** with organometallic reagents.[8] After extensive experiments[9-15] (Li-ethylenediamine,[9] sodium hydrogen telluride,[10] $LiBH_4$-MeOH/THF,[11] Ca-ethylenediamine,[12] diborane-borohydride,[13] diisobutylaluminium hydride,[14] sodium cyanoborohydride[15]) we found that the epoxide **7** was readily converted into the secondary alcohol **8** with sodium cyanoborohydride in THF. The reaction of epoxide **7** with sodium cyanoborohydride in THF at rt is a relatively slow reaction, requiring approximately 45h to complete the reaction. However, the ring-opening method of epoxide **7** with a large excess of sodium cyanoborohydride in THF at reflux temperature took 15h to give **8** without epimerization in 95% yield. Under these conditions, the epoxide **7** could easily be opened regio- and stereoselectively in high yields and neither the BOC group nor the isopropylidene group was affected. The secondary alcohol **8** was mesylated with mesyl chloride in the presence of Et_3N in CH_2Cl_2 at 0 °C to afford **9** in 98% yield. The protecting groups of isopropylidene, BOC, and TBDMS were deprotected concurrently with Dowex-50W resin (H^+ form) in 90% MeOH/water at reflux for 24h, and the ensuing cyclization with Et_3N in MeOH produced 2*R*-methyl-5*S*-hydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**1**) in 74% yield. The structure of compound **1** was determined by IR, ^1H-^1H HMQC NMR, and ^{13}C NMR.

Experimental

Methyl 2-*tert*-butoxycarbonylamino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-*D*-mannoate (2). To a solution of azido mannoate[6] (3.5 g, 11.1 mmol) in dry EtOAc (30 mL) was added 10% palladium on charcoal (350 mg) at rt under hydrogen at atmospheric pressure and the mixture was stirred for 1 h. The reaction mixture was filtered, and the filterate was evaporated at reduced pressure to afford a gel-like product. The crude product was used for the next reaction without purification.The product was dried for 1 h with vacuum pump and dissolved in MeOH (30 mL). To this solution were added triethyl amine (1.45 g, 14.4 mmol) and di-*tert*-butyl dicarbonate (3.12 g, 14.4 mmol), and the mixture was stirred at rt for 20 min. After addition of water (15 mL), the mixture was extracted three times with CH_2Cl_2 (50 mL). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography (silica gel, hexane/EtOAc, 1 : 1) gave **2** (4.02 g, 87%) as colorless oil. $[\alpha]^{20}_D$ +17.8° (c 1.03, CH_2Cl_2); IR (film) 3400, 2950, 1735, 1715, 1640, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.62 (d, 1H, *J*=7.2 Hz), 4.42 (t, 1H, *J*= 6.5 Hz), 4.17 (m, 2H), 3.76 (m, 3H), 1.47 (m, 2H), 3.76 (m, 3H), 1.42 (s, OH), 1.34 (s, 9H); Anal. Calcd for $C_{18}H_{31}NO_8$: C; 55.50, H; 8.03, N; 3.60. Found: C; 55.37, H; 8.04, N; 3.55.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-*D*-mannitol (4). To a solution of the mannoate derivative **2** (1.02 g, 2.6 mmol) in dry THF (20 mL) was added $LiAlH_4$ (0.2 g, 5.2 mmol) at 0 °C for 20 min, then the mixture was allowed to warm to rt and stirring was continued for 13 h. The reaction mixture was cooled down to 0 °C and hydrolyzed by addition of an aqueous solution of NaOH (15%, 0.5 mL) and water (1 mL). The mixture was stirred for 30 min at rt, then the mixture was filtered and filtrate was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 3 : 1) to afford **3** (0.89 g, 95.0%) as a colorless oil. This was used for the next step directly. To a solution of the crude product **3** (1.54 g, 4.3 mmol) in dry pyridine (25 mL) at rt was added acetic anhydride (0.06 mL, 6.3 mmol) for 3 min and stirring was continued for 15 h. The reaction mixture was poured into water (30 mL) and extracted three times with EtOAc (30 mL). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography (silica gel, hexane/EtOAc, 2 : 1) afforded **4** (1.60 g, 93.0%) as a white solid. $[\alpha]^{20}_D$ +4.6° (c 1.2, CH_2Cl_2); IR (film), 3425, 2900, 1770, 1710, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, *J*=7.47 Hz), 4.37 (dd, 1H, *J*=3.13, 3.30 Hz), 4.09-4.15 (m, 2H), 4.04-4.00 (m, 3H), 3.96-3.94 (m, 1H), 3.91-3.87 (m, 2H), 2.08 (s, 3H), 1.45 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H), 1.37 (d, 6H, *J*=2.56 Hz); Anal. Calcd for $C_{19}H_{33}NO_8$: C; 56.54, H; 8.25, N; 3.47. Found: C; 55.51, H; 8.18, N; 3.43.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-*D*-mannitol (5). To a solution of the acetate **4** (3.87 g, 9.6 mmol) in 90% MeOH (30 mL) was added Dowex 50W-X8 (0.5 g) and stirring was continued for 18 h at rt. The reaction mixture was filtered through a pad of Celite to remove the Dowex 50W-X8 resin and the solvent was removed *in vacuo*. Purification by flash chromatography (silica gel, hexane/EtOAc, 1 : 1) afforded **5** (3.57 g, 97.0%) as a white solid. $[\alpha]^{20}_D$ +7.2° (c 1.0, CH_2Cl_2); mp 94 °C; IR (film), 3500, 3400, 3000, 1750, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (d, 1H, *J*=

7.66 Hz), 4.33 (d, 1H, *J*=9.79 Hz), 4.20 (t, 1H, *J*=10.5 Hz), 4.12 (t, 2H, *J*=6.12 Hz), 3.97-3.94 (m, 2H), 3.82 (d, 2H, *J*= 9.04 Hz), 3.68 (s, 2H), 3.55 (s, 1H), 2.08 (s, 3H), 1.45 (s, 9H), 1.39 (d, 6H, *J*=8.47 Hz); Anal. Calcd for $C_{16}H_{29}NO_8$: C; 52.86, H; 8.05, N; 3.86. Found: C; 52.81, H; 8.01, N; 3.83.

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-6-*O*-methanesulfonyloxy-*D*-mannitol (6). To a solution of the diol **5** (3.87 g, 9.6 mmol) in dry CH_2Cl_2 (30 mL) at −10 °C was added Et_3N (0.44 mL, 3.2 mmol) for 5 min, then added methanesulfonyl chloride (0.41 mL, 5.28 mmol) and stirring was continued for 5 min. The mixture was treated with water (20 mL) and extracted three times with CH_2Cl_2 (90 mL). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography (silica gel, hexane/EtOAc, 3 : 2) afforded **6** (1.03 g, 83.0%) as a colorless oil. $[\alpha]^{20}_D$ +13.2° (c 1.0, CH_2Cl_2); IR (film), 3500, 3400, 1750, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.13 (d, 1H, *J*=14.55 Hz), 4.47 (d, 1H, *J*=22 Hz), 4.30-4.24 (m, 3H), 4.14-4.06 (m, 2H), 3.92-3.82 (m, 3H), 3.08 (s, 3H), 2.08 (s, 3H), 1.42 (s, 9H), 1.36 (d, 6H, *J*=4.4 Hz) ; Anal. Calcd for $C_{17}H_{31}NO_{10}S$: C; 46.24, H; 7.08, N; 3.17. Found: C; 46.19, H; 7.11, N; 3.12.

1-*O*-(*tert*-Butyldimethylsilyl)oxy-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-5,6-anhydro-*D*-mannitol (7). To a solution of mesylate **6** (920 mg, 2 mmol) in dry MeOH (20 mL) was added NaOH (100 mg, 3.0 mmol) and stirring was continued for 5 min at rt. The reaction mixture was treated with water (10 mL) and extracted three times with EtOAc (90 mL). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give the corresponding epoxide which was used for the next step without purification. A solution of epoxide (0.46 g, 1.7 mmol) in dry DMF (15 mL) was treated with imidazole (0.23 g, 3.39 mmol) and *tert*-butyldimethylchlorosilane (0.38 g, 2.54 mmol), and stirring was continued for 15 h at rt. The reaction mixture was treated with water (30 mL) and extracted three times with EtOAc (90 mL). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography (silica gel, hexane/EtOAc, 5 : 1) afforded **7** (0.60 g, 94.0%) as a colorless oil. $[\alpha]^{20}_D$ −5.0° (c 4.6, CH_2Cl_2); IR (film), 3450, 2960, 1730, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (d, 1H, *J*=8.90 Hz), 4.05-4.00 (m, 2H), 3.92 (d, 1H, *J*=9.84 Hz), 3.72 (dd, 2H, *J*=12.0, 3.1 Hz), 3.05 (s, 1H), 2.84 (t, 1H, *J*=4.86 Hz), 2.80-2.75 (m, 1H), 1.47 (s, 9H), 1.43 (s, 6H), 0.93 (s, 9H), 0.10 (s, 6H); Anal. Calcd for $C_{20}H_{39}NO_6Si$: C; 57.52, H; 9.42, N; 3.36. Found: C; 57.49, H; 9.41, N; 3.32.

2*R*-*tert*-Butoxycarbonylamino-3*R*,4*R*-*O*-isopropylidene-5*S*-hydroxy-1-*O*-(*tert*-butyldimethylsilyloxy)hexane (8). To a solution of epoxide 7 (330 mg, 0.85 mmol) in dry THF (5 mL) was added $NaBH_3CN$ (1 M in THF, 8.48 mL) and stirring was continued for 15 h at reflux. The reaction mixture was cooled down to rt and treated with water (10 mL) and extracted three times with EtOAc (30 mL). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography (silica gel, hexane/EtOAc, 5 : 1) afforded **8** (0.60 g, 95.0%) as a colorless oil. $[\alpha]^{20}_D$ −9.6° (c 1.7, CH_2Cl_2); IR (film), 3460, 3400, 2850-2990, 1715, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (d, 1H, *J*=6.8 Hz), 4.04 (dd, 2H, *J*=6.2, 11.3 Hz), 3.83-3.88 (m, 3H), 3.75 (dd, 2H, *J*=3.8, 9.8 Hz), 2.70 (s, OH), 1.45 (s, 9H), 1.40 (d, 6H, *J*=3.0 Hz), 1.25 (d, 3H, *J*=6.4 Hz), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$) δ −4.8, 19.0, 19.4, 26.5, 26.6, 27.7, 27.8, 27.9, 29.0, 29.1, 54.9, 63.0, 69.0, 69.1, 77.4, 77.7, 78.0, 80.4, 83.0, 109.7.

2*R*-*tert*-Butoxycarbonylamino-3*R*,4*R*-*O*-isopropylidene-5*S*-*O*-mesyl-1-*O*-(*tert*-butyldimethylsilyloxy)hexane (9). To a solution of alcohol **8** (0.1 g, 0.26 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.04 mL, 0.31 mmol) at rt and the mixture was stirred for 5 min. To the reaction mixture was added dropwise methansulfonyl chloride (0.02 mL, 0.31 mmol) at rt and stirring was continued for 10 min. The reaction mixture was treated with water (10 mL) and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 1 : 1) afforded **9** (0.11 g, 98.0%) as a colorless liquid. $[\alpha]^{20}_D$ 2.5° (c 3.1, CH_2Cl_2); IR (film), 3400, 2950, 1720, 1370 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.99 (d, 1H, *J*=9.3 Hz), 4.84-4.78 (m, 1H), 4.30 (t, 1H, *J*=6.0 Hz), 3.97 (dd, 1H, *J*=8.6, 6.7 Hz), 3.90 (d, 1H, *J*=10.0 Hz, 2.5 Hz), 3.81-3.76 (m, 1H), 3.72 (dd, 1H, *J*=3.5Hz, 9.9 Hz), 3.06 (s, 3H), 1.47 (s, 12H), 1.42 (d, 6H, *J*=6.9 Hz), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ −4.8, 17.7, 19.0, 26.5, 26.6, 27.8, 28.0, 29.1, 39.4, 55.1, 63.0, 77.4, 77.7, 78.0, 79.4, 80.6, 81.2, 110.7, 156.5.

2R-Methyl-5*S*-hydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (1). To a solution of compound **9** (132 mg, 0.31 mmol) in MeOH/water (9/1, 15 mL) was added Dowex 50W-X8 (100 mg) and stirring was continued for 24 h at reflux. The reaction mixture was filtered through a pad of Celite and the residue was washed with ammonia solution (2N, 20 mL). The solvent and ammonia solution were collected and evaporated with toluene azotropically to afford a crude product. The crude product was purified by Dowex 1-X2 (OH form) chromatography with water to afford **1** (38 mg, 74%) as white solid. mp 124 °C, $[\alpha]^{20}_D$ −43.3° (c 0.8, H_2O); IR (film), 3500-3250, 2950, 1640 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 3.93 (s, 1H), 3.87 (q, 1H, *J*=6.5 Hz), 3.68 (dd, 1H, *J*=6.2, 11.2 Hz), 3.62 (d, 1H, *J*=3.6 Hz), 3.44 (t, 1H *J*=11.2 Hz), 3.15-3.12 (m, 1H), 1.18 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (D_2O) δ 18.2, 47.9, 69.1, 72.4, 73.0, 74.1.

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Examination of Bidentate Thiol Derivatives as Ligands in the Ni-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Enones

Jahyo Kang*, Joo In Kim, Jae Hoon Lee, Hyo Jung Kim, and Yong Hun Byun

Department of Chemistry, Sogang University, Seoul 121-742, Korea
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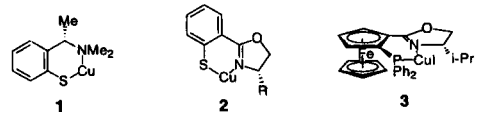
Among many highly successful asymmetric transformations, conjugate addition of alkyl group to enone lags far behind in terms of efficiency. Organocopper reagents which are the most useful reagents for racemic task have not been highly successful. Thus, development of chiral methodology which provide high levels of asymmetric induction would be especially a valuable addition. Over the last 25 years since the first attempt in 1972 by Kretchmer[1] to effect asymmetric conjugate addition of magnesium dialkylcuprates (R_2CuMgX) in the presence of (−)-sparteine with optical yield of 3-6%, many approaches have been investigated to solve the problem of asymmetric conjugate addition of organocopper reagents to α,β-unsaturated carbonyl compounds.[2,3] Despite of the increasingly important role of copper-mediated conjugate addition to α,β-enones in organic synthesis, the rather slow improvement of this methodology is associated with the fact that the mechanistic details are unclear. Furthermore, many aspects of cuprate chemistry were unknown or poorly defined such as the effect of solvent and various salts on cuprate structure and reactivity.

In this regard, notable examples are some: van Koten *et al.*[3j] described the catalytic conjugate addition using a chiral arenthiolatocopper(I) complex **1** (MeMgI, 4-phenyl-3-buten-2-one, ≤ 57% ee). Recently, is reported copper (I) thiolate complex **2** by Pfaltz (Grignard reagents, cyclopentenone (16-37% ee), cyclohexenone (60-72% ee), cycloheptenone (83-87% ee)) as enantioselective catalysts:[3e] And after our experiments were finished,[4] phosphine oxazoline complex **3** was reported by Sammakia (n-BuMgCl, cyclopentenone (65% ee), cyclohexenone (83% ee), cycloheptenone (92% ee) and 4-phenyl-3-buten-2-one (81% ee)).[3o] Even though these reactions were successful with high level of enantioselectivity, except for some cases, it was not catalytic variants but stoichiometric amount of ligand was used.



One the other hand, Ni-catalyzed asymmetric 1,4-addition reactions are also known even though the mechanism for the reaction is even more elusive than the Cu-catalyzed reactions mentioned above. Following the leads by Luche,[5] who found that Ni(II) salts facilitate the conjugate addition of dialkylzinc to enones, and by Soai who reported that enantioselective Ni(II)-catalyzed conjugate addition of dialkylzinc reagents to prochiral enones and in the presence of