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The first reductive cyclization by lithium aluminum hydride: stereospecific reductive cyclization of 1-(methoxycarbonylmethyl)imidazolidin-4-ones

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Abstract—The first $LiAlH_4$-driven reductive cyclization of the bifunctional 1-(methoxycarbonylmethyl)imidazolidin-4-ones, (−)-**1a**–**c** or (+)-**1a**–**c**, stereospecifically generated the corresponding 1,6-diaza-4-oxa-bicyclo[3.2.1]octanes, (−)-**3a**–**c** or (+)-**3a**–**c**, with a novel bicyclic system.

Lithium aluminum hydride is one of the well-known hydride-transfer reducing agents and reduces several commonly encountered organic functional groups.[1] Because this reagent shows very high reducing power, it does not appear to be very selective.[1]

We treated 1-(methoxycarbonylmethyl)imidazolidin-4-one (−)-**1a**[2] with $LiAlH_4$ in anhydrous ether at room temperature for one day in order to prepare novel chiral β-amino alcohols, but the isolated product was unexpected 1,6-diaza-4-oxa-bicyclo[3.2.1]octane (−)-**3a** (Scheme 1). To our knowledge, the bicyclic ring system of (−)-**3a** is new. One may argue that the bridged *N*,*O*-acetal **6** like (−)-**3a** can be prepared from 1-(2-hydroxyethyl)imidazolidine **5** by intramolecular addition of the hydroxyl group to the imine group (Scheme 2). However, in the presence of $LiAlH_4$, the imine group of **5** is reduced much faster than intramolecular addition of the hydroxyl group to the imine group, so the bridged *N*,*O*-acetal **6** cannot be produced.[1] That is why reduction of many bifunctional compounds by $LiAlH_4$ has not generated cyclic products. In this letter, we show this novel observation by demonstrating the first example of the reductive cyclization carried out by $LiAlH_4$ and explain how it works.

When (−)-**1a** was treated with $LiAlH_4$ in anhydrous ether at room temperature, some reaction mixture was taken out for ^1H NMR spectra analysis during the reaction. The ^1H NMR spectra analysis showed that the reaction mixture contained some reductive cyclization product (−)-**3a** and some intermediate (*S*,*R*)-**2a** involving reduction of ester group only (Scheme 1). After the reaction was complete, high yield of the reductive cyclization product (−)-**3a** was obtained at the expense of the intermediate (*S*,*R*)-**2a**, indicating that (*S*,*R*)-**2a** is an intermediate to the reductive cyclization product. Amide group of (*S*,*R*)-**2a** is not activated enough to be subject to the intramolecular attack of the hydroxyl group. It was reported that imine or iminium ion is formed as an intermediate when $LiAlH_4$ reduces an amide.[3] It is likely that during the reduction process the hydroxyl group of (*S*,*R*)-**2a** competes with hydride of $LiAlH_4$ to attack the resulting iminium intermediate, which is formed from reduction of the amide group of (*S*,*R*)-**2a** by $LiAlH_4$. When the former process is faster than the latter, the reductive cyclization product (−)-**3a** is formed. The product is quite stable, indicating that the intramolecular addition of the hydroxyl group of (*S*,*R*)-**2a** to the iminium group is irreversible. After this reaction was complete, (−)-**3a**[4] was formed highly diastereoselectively and (*S*,*S*,*R*)-**4a** could not be found by NMR spectrometry, indicating that the hydroxyl group of (*S*,*R*)-**2a** preferred to attack *Re* face of the resulting

Keywords: Reductive cyclization; Lithium aluminum hydride; Stereospecific reaction.
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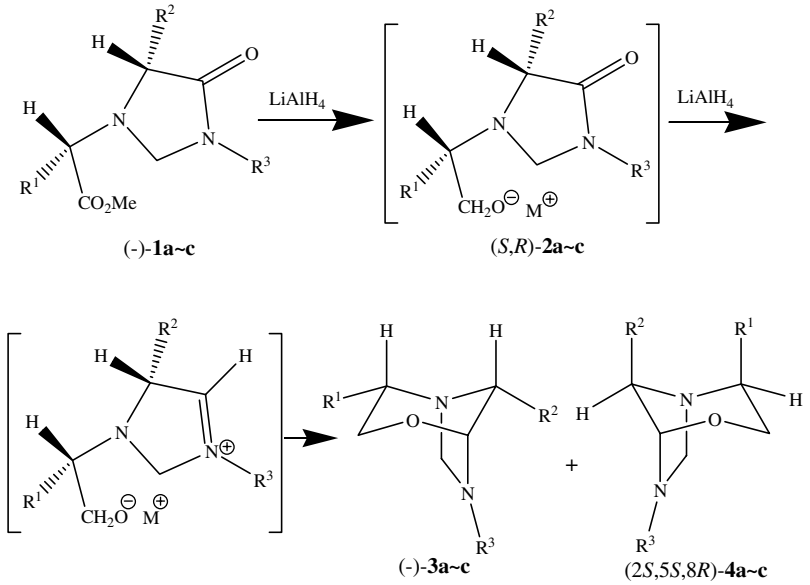
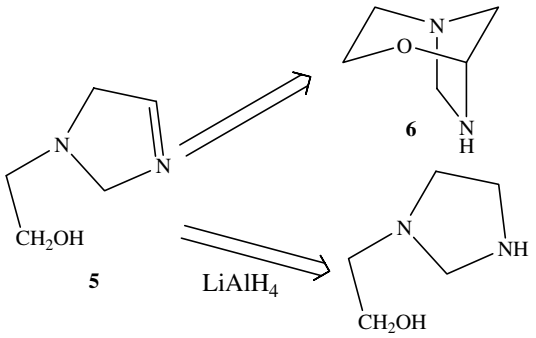


a: R^1: *i*-Pr, R^2: $(C_2H_5)CH$, R^3: *p*-tolyl; **b**: R^1: *i*-Pr, R^2: *i*-Pr, R^3: *p*-tolyl;

c: R^1: *i*-Pr, R^2: ferrocenyl, R^3: *p*-tolyl

Scheme 1.



Scheme 2.

iminium group. It is clear that the bulky groups stay at equatorial positions preferentially during the cyclization process, leading to the high diastereoselectivity.

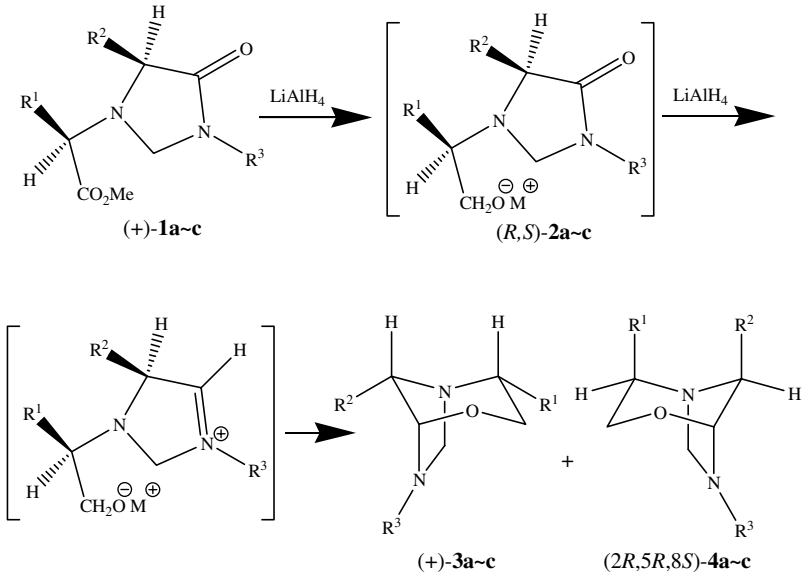
The bifunctional compound (−)-**1b** with $R^2 = i$-Pr group, which is less bulky than $(C_2H_5)_2CH$ group in (−)-**1a**, was treated with $LiAlH_4$ in anhydrous ether at room temperature for one day. Yield of the reductive cyclization product (−)-**3b**[5] is not high, and the major by-product is the one involving reduction of both ester and amide groups without cyclization, indicating that the rates for both hydride of $LiAlH_4$ and the hydroxyl group of (*S*,*R*)-**2b** to attack the resulting iminium group are comparable. When we did this reaction at 0 °C for 3 days, yield of the reductive cyclization significantly improved and the amount of the major byproduct was greatly reduced. At temperatures lower than 0 °C, the reaction was too slow to be useful. Therefore, we applied this optimal reaction condition[6] to the reductive cyclization of other bifunctional compounds, and the results are shown in Table 1.

When reductive cyclization of (+)-**1a** was carried out with $LiAlH_4$, (+)-**3a** was formed highly diastereoselectively and (*R*,*R*,*S*)-**4a** could not be found by NMR spectrometry, indicating that the hydroxyl group of (*R*,*S*)-**2a** preferred to attack *Si* face of the resulting iminium group and the high diastereoselectivity is caused by preferential equatorial positions for bulky groups during the cyclization process (Scheme 3). Clearly the reductive cyclization reactions of (−)-**1a**–**c** and (+)-**1a**–**c** with $LiAlH_4$ are stereospecific (Schemes 1 and 3).

Table 1. Reductive cyclization of (−)-**1a**–**c** and (+)-**1a**–**c** with $LiAlH_4$

Reactant	R^1	R^2	R^3	Product (yield[a] (%))	(−)-**3**:(*S*,*S*,*R*)-**4**	(+)-**3**:(*R*,*R*,*S*)-**4**
(−)-**1a**	*i*-Pr	$(C_2H_5)_2CH$	*p*-Tolyl	(−)-**3a** (86)	100:0	
(+)-**1a**	*i*-Pr	$(C_2H_5)_2CH$	*p*-Tolyl	(+)-**3a** (89)		100:0
(−)-**1b**	*i*-Pr	*i*-Pr	*p*-Tolyl	(−)-**3b** (91)	100:0	
(+)-**1b**	*i*-Pr	*i*-Pr	*p*-Tolyl	(+)-**3b** (84)		100:0
(−)-**1c**	*i*-Pr	Ferrocenyl	*p*-Tolyl	(−)-**3c** (87)	100:0	
(+)-**1c**	*i*-Pr	Ferrocenyl	*p*-Tolyl	(+)-**3c** (87)		100:0

[a] Isolated yield.



a: R^1: *i*-Pr, R^2: $(C_2H_5)CH$, R^3: *p*-tolyl; **b**: R^1: *i*-Pr, R^2: *i*-Pr, R^3: *p*-tolyl;

c: R^1: *i*-Pr, R^2: ferrocenyl, R^3: *p*-tolyl

Scheme 3.

Reductive cyclization of (−)-**1c** or (+)-**1c** with R^2 = bulky ferrocenyl group by $LiAlH_4$ also worked very well to produce the corresponding (−)-**3c**[7] or (+)-**3c**. On the other hand, when we did reductive cyclization of (−)-**1** and (+)-**1** with R^3 = alkyl group like cyclohexyl at 0 °C by $LiAlH_4$, very little reductive cyclization product was obtained. The major product was the one involving reduction of both ester and amide groups without cyclization, indicating that electronic effect of R^3 plays an important role on this reductive cyclization.

The bicyclic structure of the reductive cyclization products, (−)-**3a**–**c** or (+)-**3a**–**c**, can be confirmed by proton NMR, HMQC, and HMBC spectra. One representative example for (−)-**3b** is demonstrated as follows, and its HMBC spectrum is shown in Figure 1. Chemical shift of H^1 located on C^1 (δ 82.79) is δ 5.24 as a singlet, which is coupled with C^2 (δ 79.38), C^4 (δ 62.74) and C^5 (δ 63.33). Chemical shift of H^2 located on C^2 (δ 79.38) is δ 2.75 as a doublet (J = 10.6 Hz), which is coupled with C^1 (δ 82.79), C^3 (δ 69.03) and C^5 (δ 63.33). Chemical shift of H^3 located on C^3 (δ 69.03) is δ 2.58 as a doublet of doublet of doublet (J = 11.8, 11.8, 4.8 Hz), which is coupled with C^4 (δ 62.74) and C^5 (δ 63.33). Chemical shift of H^{4e} located on C^4 (δ 62.74) is δ 3.66 as a doublet of doublet (J = 4.8, 11.8 Hz), which is coupled with C^1 (δ 82.79). Chemical shift of H^{4a} located on C^4 (δ 62.74) is δ 3.08 as a doublet of doublet (J = 11.8, 11.8 Hz), which is coupled with C^3 (δ 69.03). Chemical shift of H^{5L} located on C^5 (δ 63.33) is δ 4.02 as a doublet (J = 8.4 Hz), which is coupled with C^2 (δ 79.38) and C^3 (δ 69.03). Chemical shift of H^{5R} located on C^5 (δ 63.33) is δ 4.18 as a doublet (J = 8.4 Hz), which is coupled with C^3 (δ 69.03).

Compound **7**, whose structure is very close to that of the reductive cyclization product (−)-**3a**, was optimized at B3LYP/6-31+G* level and its structure is shown in Scheme 4 and Figure 2.[8] The dihedral angle of H(10)–C(5)–C(4)–H(15) is 79°, and that does not allow H(15) to couple with H(10) in the proton NMR spectrum according to the vicinal Karplus correlation.[9] This is consistent with the experimental results that H(15) is a singlet in the ^1H NMR spectra of (−)-**3a**–**c** or (+)-**3a**–**c**.

The $LiAlH_4$-driven reduction of bifunctional compound **8**, whose structure is similar to that of (−)-**1a** except that its amide group is not in a five-membered ring, did not generate a reductive cyclization product but produced a product involving reduction of both ester and amide groups without cyclization, implying that the five-membered ring, imidazolidin-4-one, makes (−)-**1a** more rigid and the rigid system makes the bulky R^2 group efficiently protect the resulting iminium group from attacking by $LiAlH_4$ (Scheme 4). All the reductions of bifunctional compounds **9**, **10**, and **11** with $LiAlH_4$ generated the corresponding products whose ester and amide groups were reduced without cyclization, and these results confirm that a bulky group is needed to protect the resulting iminium group from attacking by $LiAlH_4$.

In conclusion, to make the $LiAlH_4$-driven reductive cyclization to be successfully applied to the bifunctional ester/amide compounds, the bifunctional compounds need a bulky substituent to efficiently protect the generated iminium intermediate from attacking by $LiAlH_4$, and *N*-aryl group is needed for the functional group of amide.

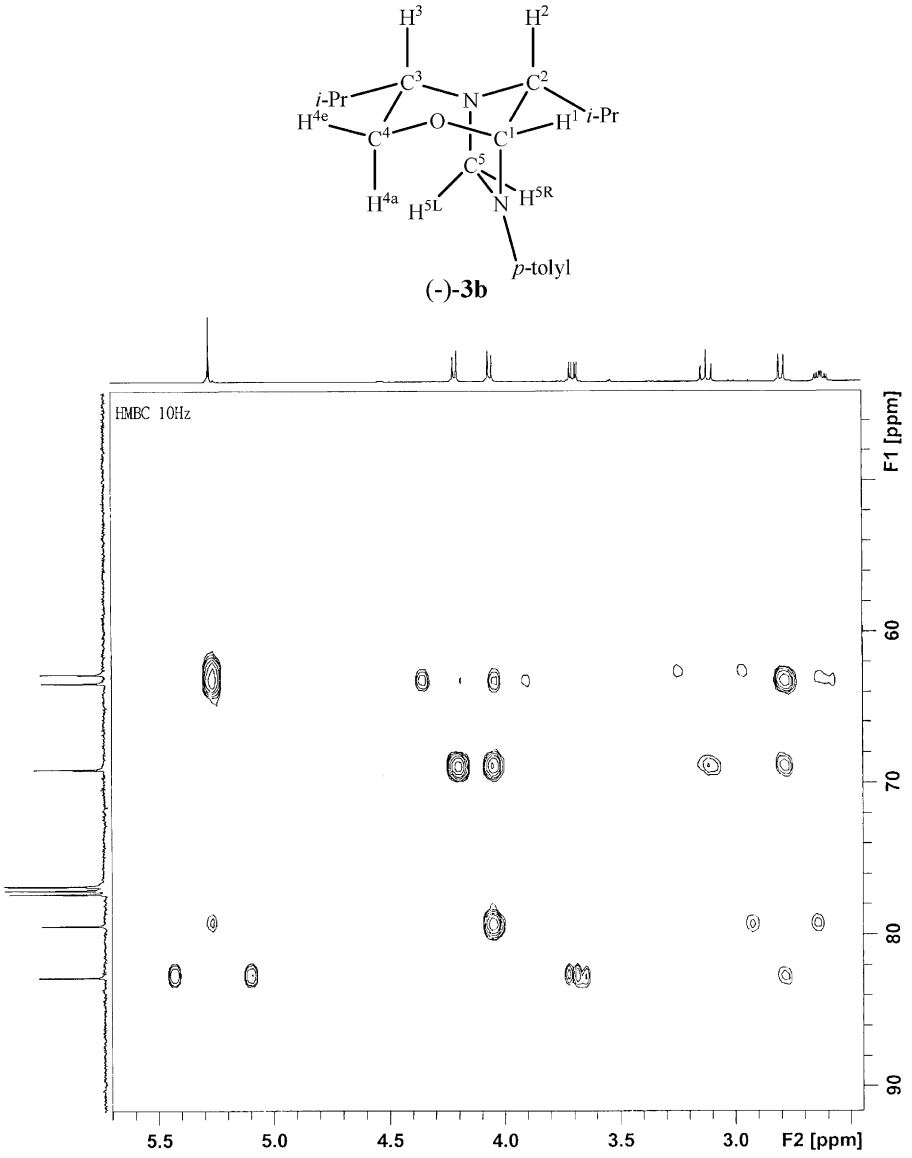
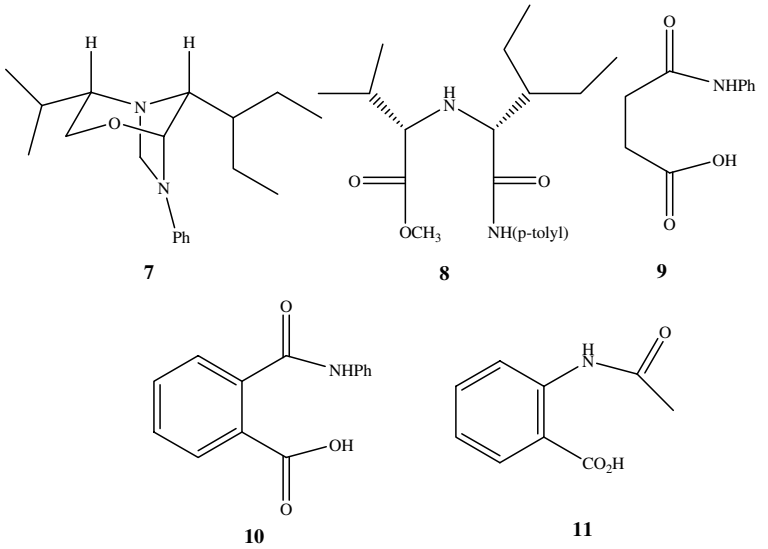


Figure 1. HMBC of (−)-**3b**.



Scheme 4.

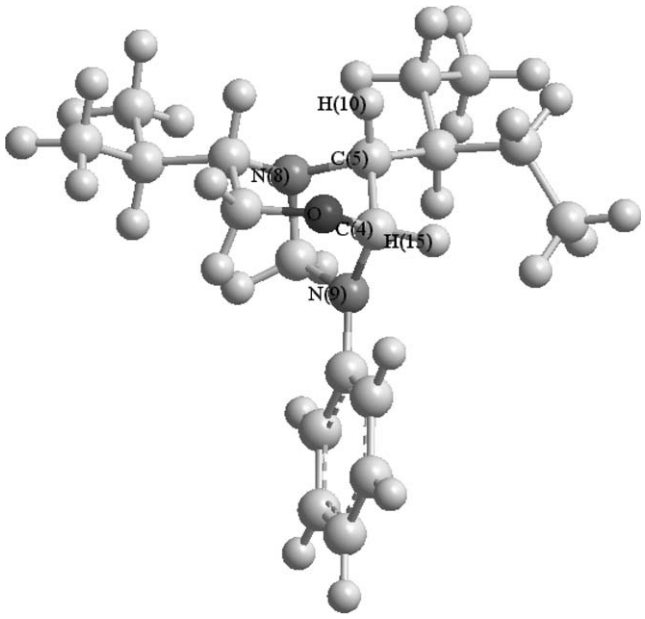


Figure 2. Optimized structure of **7** at level of B3LYP/6-31+G*.

Acknowledgements

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4. Characterization of (−)-**3a**: $[\alpha]_D^{20}$ −6.35 (*c* 0.0165 g/mL, ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 0.77 (3H, d, $J = 6.5$ Hz, CH_3), 0.86 (6H, t, $J = 7.2$ Hz, CH_3), 1.06 (3H, d, $J = 6.5$ Hz, CH_3), 1.30 (4H, m, CH_2), 1.44 (1H, m, CH), 1.57 (1H, m, CH), 2.28 (3H, s, CH_3), 2.59 (1H, ddd, $J = 11.7$, 11.7, 4.8 Hz, CH), 2.99 (1H, d, $J = 10.1$ Hz, CH), 3.10 (1H, dd, $J = 11.7$, 11.7 Hz, CH), 3.68 (1H, dd, $J = 11.7$, 4.8 Hz, CH), 4.04 (1H, d, $J = 8.4$ Hz, CH), 4.19 (1H, d, $J = 8.4$ Hz, CH), 5.24 (1H, s, CH), 6.67 (2H, d, $J = 8.4$ Hz, PhH), 7.07 (2H, d, $J = 8.4$ Hz, PhH); ^{13}C NMR ($CDCl_3$): δ 9.34, 10.51, 19.03, 19.80, 19.96, 20.07, 21.66, 29.42, 36.60, 62.69, 63.22, 69.07, 75.34, 83.17, 112.64, 126.77, 129.73, 141.60; IR (hexane) 1621, 1519 (C=C) cm^{-1}; HRMS (ESI,M+1) *m*/*z* calcd for $C_{20}H_{33}N_2O$ 317.2593, found 317.2593.
5. Characterization of (−)-**3b**: $[\alpha]_D^{20}$ −33.58 (*c* 0.0268 g/mL, ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 0.76 (3H, d, $J = 6.8$ Hz, CH_3), 0.92 (3H, d, $J = 6.4$ Hz, CH_3), 0.99 (3H, d, $J = 6.4$ Hz, CH_3), 1.05 (3H, d, $J = 6.8$ Hz, CH_3), 1.45 (1H, m, CH), 1.52 (1H, m, CH), 2.27 (3H, s, CH_3), 2.58 (1H, ddd, $J = 11.8$, 11.8, 4.8 Hz, CH_3), 2.75 (1H, d, $J = 10.6$ Hz, CH_3), 3.08 (1H, dd, $J = 11.8$, 11.8 Hz, CH), 3.66 (1H, dd, $J = 11.8$, 4.8 Hz, CH), 4.02 (1H, d, $J = 8.4$ Hz, CH), 4.18 (3H, d, $J = 8.4$ Hz, CH), 5.24 (1H, s, CH), 6.66 (2H, d, $J = 8.3$ Hz, PhH), 7.06 (2H, d, $J = 8.3$ Hz, PhH); ^{13}C NMR ($CDCl_3$): δ 19.12, 19.14, 19.85, 20.10, 20.36, 25.65, 29.52, 62.74, 63.33, 69.03, 79.38, 82.79, 112.69, 126.86, 129.77, 141.68; IR (hexane) 1617, 1521 (C=C) cm^{-1}; HMRS(ESI, M+1) *m*/*z* calcd for $C_{18}H_{29}N_2O$ 289.2280, found 289.2281.
6. General method for the reductive cyclization of (+)-**1a**–**c** and (−)-**1a**–**c**: To a solution of (−)-**1a**–**c** or (+)-**1a**–**c** (1 mmol) in 3 mL of anhydrous ether was added lithium aluminum hydride (4 mmol). The mixture was stirred under nitrogen atmosphere at 0 °C for 3 days. After the reaction was complete, the mixture was quenched by water and extracted with ethyl acetate. The ethyl acetate solution was dried with anhydrous Na_2SO_4 and concentrated by rotary evaporator. The residue was purified by column chromatography with a mobile phase of 25% ethyl acetate in hexanes to get (−)-**3a**–**c** or (+)-**3a**–**c**.
7. Characterization of (−)-**3c**: $[\alpha]_D^{20}$ −4.6 (*c* 0.001 g/mL, acetonitrile); ^{1}H NMR ($CDCl_3$): δ0.79 (3H, d, $J = 6.5$ Hz, CH_3), 1.02 (3H, d, $J = 6.5$ Hz, CH_3), 1.44 (1H, m, CH), 2.29 (3H, s, CH_3), 2.79 (1H, ddd, $J = 11.8$, 11.8, 4.7 Hz, CH_3), 3.20 (1H, dd, $J = 11.8$, 11.8 Hz, CH), 3.74 (1H, dd, $J = 11.8$, 4.7 Hz, CH), 3.98 (2H, d, $J = 8.0$ Hz, CH on CP), 4.12 (1H, d, $J = 8.5$ Hz, CH on CP), 4.14 (5H, s, CH on CP), 4.15–4.20 (3H, m, CH and CH on CP), 4.32 (1H, s, CH), 5.46 (1H, s, CH), 6.70 (2H, d, $J = 8.0$ Hz, PhH), 7.09 (2H, d, $J = 8.0$ Hz, PhH); ^{13}C NMR ($CDCl_3$): δ 19.31, 20.30, 20.41, 29.63, 62.77, 62.88, 67.24, 67.83, 68.27, 68.49, 68.62, 69.16, 71.97, 76.57, 77.00, 77.20, 77.42, 83.32, 84.66, 112.65, 127.07, 129.95, 141.00; IR (hexane) 1627, 1520 (C=C) cm^{-1}; HMRS(ESI, M+1) *m*/*z* calcd for $C_{25}H_{31}N_2OFe$ 431.1786, found 431.1784.
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