Journal of Fluorine Chemistry 129 (2008) 994–997

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Short communication

Asymmetric intramolecular Cannizzaro reaction of anhydrous phenylglyoxal

Kazuaki Ishihara *, Takayuki Yano, Makoto Fushimi

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan

ARTICLE INFO

Article history:
Received 16 March 2008
Received in revised form 24 April 2008
Accepted 25 April 2008
Available online 2 May 2008

Keywords:
Copper(II) hexafluoroantimonate
Intramolecular Cannizzaro reaction
Phenylglyoxal
Double asymmetric induction
Anhydrous
Bis(oxazoline)

ABSTRACT

The use of anhydrous phenylglyoxal provides a solution to the problem of low reactivity in the asymmetric intramolecular Cannizzaro reaction with alcohols. Double asymmetric induction was achieved in the reaction of anhydrous phenylglyoxal with D-(+)-menthol promoted by a (*S*,*S*)-*t*-BuBox·copper(II) hexafluoroantimonate complex.

1. Introduction

We have recently achieved a highly efficient synthesis of carboxamides by lithium *N*,*N*-diisopropylamide (LDA)-catalyzed Haller–Bauer and Cannizzaro-type reactions of ketones and aldehydes with lithium *N*-alkylamides and lithium *N*,*N*-dialkylamides [1]. Phenylglyoxal (**1**) is a typical substrate for the intramolecular Cannizzaro-type reaction. However, commercial phenylglyoxal monohydrate [**1**·H_2O] is not suitable for the LDA-catalyzed intramolecular Cannizzaro-type reaction with lithium pyrrolidinide because of the presence of water. Anhydrous **1** is unstable at high concentration, and readily oligomerizes. This problem has been overcome by the use of a ca. 1 M solution of anhydrous **1** in toluene, which is prepared from its hydrate by the removal of water under azeotropic reflux conditions in toluene. We have confirmed that a solution of anhydrous **1** in toluene can be preserved for more than several months in the refrigerator (Scheme 1).

Earlier, Morken et al. reported the catalytic enantioselective Cannizzaro reaction of arylglyoxal hydrates in a 2:1 mixed solvent of 2-propanol–1,2-dichloroethane [2]. For instance, in the presence of 10 mol% each of (*S*,*S*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) [(*S*,*S*)-PhBox (**3a**)] and $Cu(OTf)_2$, **1**·H_2O is converted to (*R*)-isopropyl mandelate (**2a**) in 57% yield with 28% ee (Scheme 2). Large excess amounts of alcohols are required in the above reaction, probably because water decreases the Lewis acidity of $Cu(OTf)_2$. Thus, we were interested in whether anhydrous arylglyoxals could be used for the Lewis acid-catalyzed Cannizzaro reaction. Furthermore, we expected that more cationic and bulky Lewis acids such as $Cu(NTf_2)_2$ and $Cu(SbF_6)_2$ might be more efficient catalysts for the enantioselective reaction because of the strong electronegativity of fluorine substituents.

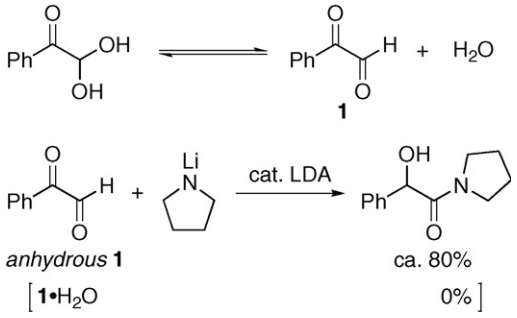
We report here the asymmetric intramolecular Cannizzaro reaction of anhydrous phenylglyoxal with alcohols to give optically active alkyl α-hydroxyphenylacetates induced by chiral bis(oxazoline)·CuX_2 catalysts.

2. Results and discussion

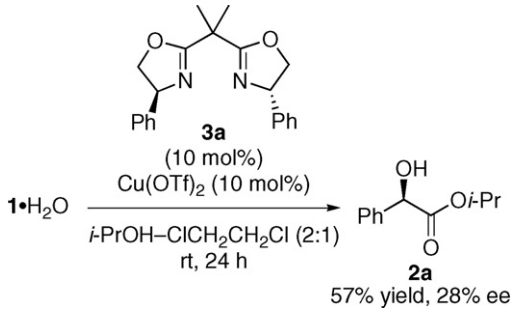
Based on Morken's paper [2], we examined the intramolecular Cannizzaro reaction of anhydrous phenylglyoxal **1** with just two equivalents of isopropanol in the presence of 10 mol% of (*R*,*R*)-**3a**·$Cu(OTf)_2$ in 1,2-dichloroethane at room temperature (entry 1, Table 1). As expected, the reaction proceeded more smoothly to give (*S*)-isopropyl mandelate **2a** in 89% yield. However, the enantioselectivity was quite low (23% ee), as in Morken's report [2]. Although (*R*,*R*)-**3a**·$Cu(SbF_6)_2$ was also examined, the reaction did not proceed due to the decomposition of (*R*,*R*)-PhBox ligand (entry 2). Evans et al. previously reported that (*R*,*R*)-**3a**·$Cu(SbF_6)_2$ is very unstable due to the strong Lewis acidity of $Cu(SbF_6)_2$ [3a]. Fortunately, the enantioselectivity was improved to 42% ee with the use of *tert*-butanol instead of isopropanol in the presence of 10 mol% of (*R*,*R*)-**3a**·$Cu(OTf)_2$, although the chemical yield of (*S*)-**2b** was reduced to 18% (entry 3).

* Corresponding author. Tel.: +81 52 789 3331; fax: +81 52 789 3222.
E-mail address: ishihara@cc.nagoya-u.ac.jp (K. Ishihara).

0022-1139/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2008.04.008



Scheme 1.



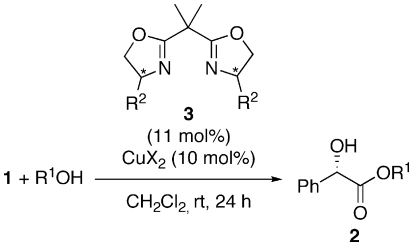
Scheme 2.

Next, (*S*,*S*)-2,2′-isopropylidenebis(4-*tert*-butyl-2-oxazoline) [(*S*,*S*)-*t*-BuBox (**3b**)] was examined instead of (*R*,*R*)-**3a** because of strong tolerance of **3b** to $Cu(NTf_2)_2$ and $Cu(SbF_6)_2$. Surprisingly, the (*S*,*S*)-**3b**·$Cu(OTf)_2$-catalyzed reaction of **1** with isopropanol gave (*S*)-**2a** as a major enantiomer. However, the enantioselectivity was low (15% ee) (entry 4). The use of $Cu(SbF_6)_2$ gave slightly better reactivity and enantioselectivity than with $Cu(OTf)_2$ and $Cu(NTf_2)_2$ (entries 4–6). The use of *tert*-butanol instead of isopropanol in the presence of 10 mol% of (*S*,*S*)-**3b**·$Cu(OTf)_2$ also increased the enantioselectivity to 53% ee (entry 7). The chemical yield of **2b** increased from 11% to 42% with the use of 53 equiv of *tert*-butanol (entry 8). Thus, **2b** was obtained in 71% yield with 54% ee under optimized conditions with the use of 53 equiv of *tert*-butanol in the presence of 10 mol% of (*S*,*S*)-**3b**·$Cu(SbF_6)_2$ (entry 9).

To develop a highly enantioselective intramolecular Cannizzaro reaction, we examined double asymmetric induction in the **3**·CuX_2-catalyzed reaction of anhydrous phenylglyoxal **1** with (+)- or (−)-menthol. As shown in Table 2, the reaction of **1** with D-(+)-menthol (2 equiv.) in the presence of 10 mol% of (*R*,*R*)-**3a**·$Cu(OTf)_2$ gave D-(+)-menthyl (*S*)-mandelate (**2c**) in 72% yield with 77% de (entry 1). On the other hand, the reaction of **1** with L-(−)-menthol (2 equiv.) in the presence of 10 mol% of (*R*,*R*)-**3a**·$Cu(OTf)_2$ gave L-(−)-menthyl (*R*)-mandelate (**2c**) in 81% yield with 35% de (entry 2). As expected, double asymmetric induction was observed when D-(+)-menthol and (*R*,*R*)-**3a** were used for the reaction of **1**. This result was much better than that using *tert*-butanol and (*R*,*R*)-**3a** (see Table 1, entry 2). Furthermore, the chemical yield and diastereoselectivity of **2c** were increased to 81% and 90% de with the use of D-(+)-menthol and (*S*,*S*)-**3b**·$Cu(SbF_6)_2$ (entry 3).

Based on the stereochemical outcome of these reactions, we propose a plausible mechanism (Scheme 3) to rationalize the observed absolute configuration of the products. According to the mechanism proposed by Morken and co-workers [2], the initial reaction of **1** with *tert*-butanol provides hemiacetal. Subsequent coordination of the hemiacetal to chiral **3**·CuX_2 followed by intramolecular hydride transfer, presumably by a three-center transition state, might then provide the observed reaction product **2b**. Enantioselective transformation would result from dynamic resolution whereby the chiral **3**·CuX_2 selectively chelates and catalyzes the rearrangement of one enantiomer of a racemic equilibrating mixture of the hemiacetal. However, neither we nor Morken et al. can rule out the enantioselective addition of *tert*-butanol to Cu(II)-coordinated **1** as a mechanism for enantioselective transformation. Steric interactions that would govern this

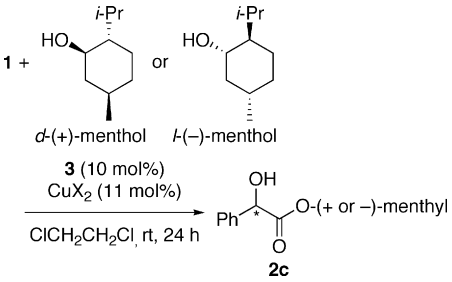
Table 1
3·CuX_2-catalyzed enantioselective intramolecular Cannizzaro reaction of anhydrous phenylglyoxal **1**[a]



Entry	**3** [R^2]	CuX_2	R^1OH (equiv)	**2**	
				Yield (%)	ee (%) [configuration]
1	(*R*,*R*)-**3a** [Ph]	$Cu(OTf)_2$	*i*-PrOH, 2	**2a**, 89	23 [*S*]
2	(*R*,*R*)-**3a** [Ph]	$Cu(SbF_6)_2$	*i*-PrOH, 2	**2a**, trace	0
3	(*R*,*R*)-**3a** [Ph]	$Cu(OTf)_2$	*t*-BuOH, 2	**2b**, 18	42 [*S*]
4	(*S*,*S*)-**3b** [*t*-Bu]	$Cu(OTf)_2$	*i*-PrOH, 2	**2b**, 85	15 [*S*]
5	(*S*,*S*)-**3b** [*t*-Bu]	$Cu(NTf_2)_2$	*i*-PrOH, 2	**2b**, 80	17 [*S*]
6	(*S*,*S*)-**3b** [*t*-Bu]	$Cu(SbF_6)_2$	*i*-PrOH, 2	**2b**, 87	20 [*S*]
7	(*S*,*S*)-**3b** [*t*-Bu]	$Cu(OTf)_2$	*t*-BuOH, 2	**2b**, 11	53 [*S*]
8	(*S*,*S*)-**3b** [*t*-Bu]	$Cu(OTf)_2$	*t*-BuOH, 53	**2b**, 42	53 [*S*]
9[b]	(*S*,*S*)-**3b** [*t*-Bu]	$Cu(SbF_6)_2$	*t*-BuOH, 53	**2b**, 71	54 [*S*]

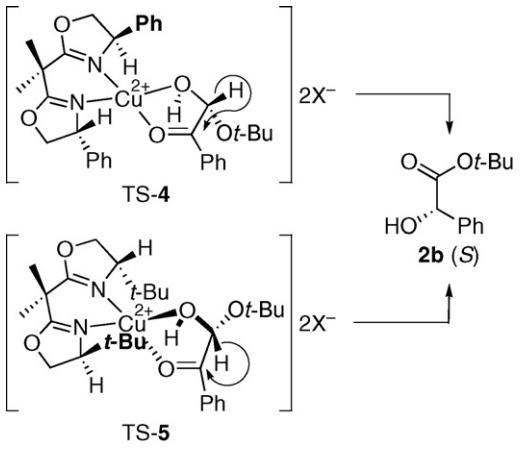
[a] Unless otherwise noted, the Cannizzaro reaction of **1** (1 equiv.) with R^1OH (2 or 53 equiv.) was conducted in 1,2-dichloroethane in the presence of **3**·CuX_2 (10 mol%) at room temperature.
[b] Dichloromethane was used instead of 1,2-dichloroethane.

Table 2
Double asymmetric induction in the **3**·CuX_2-catalyzed intramolecular Cannizzaro reaction of anhydrous phenylglyoxal **1** with (+ or −)-menthol[a]



Entry	**3** [R^2]	CuX_2	R^1OH	**2c**	
				Yield (%)	de (%) [configuration][b]
1	(*R*,*R*)-**3a** [Ph]	$Cu(OTf)_2$	D-(+)-menthol	72	77 [*S*]
2	(*R*,*R*)-**3a** [Ph]	$Cu(OTf)_2$	L-(−)-menthol	81	35 [*R*]
3[c]	(*S*,*S*)-**3b** [*t*-Bu]	$Cu(SbF_6)_2$	D-(+)-menthol	81	90 [*S*]

[a] Unless otherwise noted, the Cannizzaro reaction of **1** with L- or D-menthol (2 equiv.) was conducted in 1,2-dichloroethane in the presence of **3**·CuX_2 (10 mol%) at room temperature.
[b] The absolute configuration of the mandelic moiety of **2c** is shown in brackets.
[c] Dichloromethane was used instead of 1,2-dichloroethane.



Scheme 3.

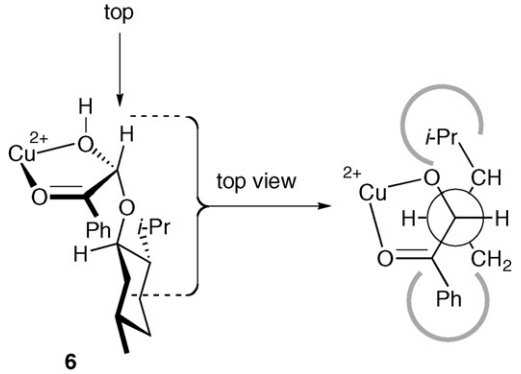


Fig. 1. Predicted most thermodynamically stable Cu(II)-chelated complex **6** with a hemiacetal derived from **1** and D-(+)-menthol.

addition process should be similar to those proposed for binding of the chiral metal complex to hemiacetal. Thus, the nature of the observed preference for the (*S*) abolute configuration in product **2b** can be understood through TS-**4** and TS-**5**, which are proposed for the Cannizzaro reactions of **1** with *tert*-butanol catalyzed by (*R*,*R*)-**3a**·CuX_2 and (*S*,*S*)-**3b**·CuX_2, respectively. TS-**4** is a square planar complex in which the *t*-BuO group is directed away from the steric bulk of the Ph group (shown in bold in Scheme 3) [3a,b]. On the other hand, TS-**5** is a twisted square planar (pseudo-tetrahedral) complex in which the *t*-BuO group is directed away from the steric bulkiness of the *t*-Bu group (shown in bold in Scheme 3) [3a,b].

The most thermodynamically stable Cu(II)-chelated complex **6** with hemiacetal derived from **1** and D-(+)-menthol can also be predicted due to the minimized steric hindrance between the *i*-Pr group and the Ph group, as shown in Fig. 1. The absolute configuration of the anomeric carbon of **6** is the same as those of TS-**4** and TS-**5**. Therefore, double asymmetric induction would be observed in the reactions of **1** with D-(+)-menthol catalyzed by (*R*,*R*)-**3a**·CuX_2 and (*S*,*S*)-**3b**·CuX_2.

3. Conclusion

Chiral Lewis acid-catalyzed intramolecular Cannizzaro reaction of **1** with alcohols proceeded more smoothly under anhydrous conditions. **3b**·$Cu(SbF_6)_2$ was a more active and selective chiral Lewis acid catalyst than **3a**·$Cu(OTf)_2$ for the Cannizzaro reaction. Thus, the enantioselectivity and chemical yield of product **2** were improved to 54% ee and 71% under our optimized conditions (for the previous results, see Scheme 2). Furthermore, we succeeded in the double asymmetric induction of the Cannizzaro reaction of **1** with D-(+)-menthol catalyzed by (*S*,*S*)-**3b**·$Cu(SbF_6)_2$ to give (*S*)-**2c** in 81% yield with 90% de. (*S*)-**2c** can be hydrolyzed to (*S*)-mandelic acid and D-(+)-menthol. The extremely steric bulkiness and the delocalized electronagativity of SbF_6^- were important as a counter anion of **3b**·copper(II).

4. Experimental

^1H NMR spectra were measured on Varian Gemini-2000 (300 MHz) spectrometer at ambient temperature. Data were

recorded as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). Acetonitrile was dried over molecular sieves 3 Å. 1,2-Dichloroethane and dichloromethane were freshly distilled from calcium hydride. Isopropanol and *tert*-butanol were distilled from calcium hydride and stored over molecular sieves 3 Å. Other simple chemicals were analytical-grade and obtained commercially.

4.1. Preparation of anhydrous phenylglyoxal 1 in toluene [1]

A 10-mL, single-necked, pear-shaped-flask equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with commercially available phenylglyoxal hydrate (152 mg, 1 mmol) and toluene (2.5 mL). The mixture was heated to azeotropic reflux with the removal of water. After being stirred for 1 h, the resulting mixture was cooled to ambient temperature.

4.2. Preparation of a $Cu(OTf)_2$·**3** catalyst solution

To a flame-dried flask were added **3** (0.11 mmol), $Cu(OTf)_2$ (36.2 mg, 0.10 mmol) and 1,2-dichloromethane (2 mL). The mixture was stirred at room temperature for 3 h.

4.3. Preparation of a $Cu(SbF_6)_2$·**3b** catalyst solution

To a flame-dried flask were added (*S*,*S*)-**3b** (32.4 mg, 0.11 mmol), $CuBr_2$ (22.3 mg, 0.10 mmol), $AgSbF_6$ (37.8 mg, 0.11 mmol) and dichloromethane (4 mL). The mixture was filtered through a syringe filter.

4.4. General procedure for the enantioselective intramolecular Cannizzaro reaction of anhydrous 1 with alcohol induced by 3·CuX_2 catalyst

To a solution of **3**·CuX_2 (0.10 mmol) were added anhydrous **1** (1 mmol, 1 M in toluene) and alcohol. The mixture was stirred at room temperature for 24 h. The reaction was quenched with 1 M HCl aqueous solution at room temperature. The products were extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (hexane–EtOAc) afforded desired product **2**.

- Isopropyl (*S*)-2-hydroxy-2-phenylacetate (**2a**) [2]: The ee was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane–*i*-PrOH = 80:1 for elution, flow rate = 1.0 mL/min; λ = 205 nm) t_R = 10.6 min for (*S*)-**2a**, 20.1 min for (*R*)-**2a**.
- *tert*-Butyl (*S*)-2-hydroxy-2-phenylacetate (**2b**) [4]: The ee was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane–*i*-PrOH = 20:1 for elution, flow rate = 1.0 mL/min; λ = 206 nm) t_R = 5.8 min for (*S*)-**2b**, 9.9 min for (*R*)-**2a**.
- D-Menthyl (*S*)-2-hydroxy-2-phenylacetate (**2c**) [5]: The de was determined by ^{1}H NMR analysis ($CDCl_3$, 300 MHz): d 4.65 (dt, *J* = 4.5, 10.8 Hz, 1H, (*S*)-**2c**) and 4.77 (dt, *J* = 4.5, 10.8 Hz, 1H, (*R*)-**2c**).

Acknowledgements

Financial support for this project was provided by the Toray Science Foundation and the G-COE in Chemistry, Nagoya. We thank Ms. Sayaka Tanahara for her help with the experiments.

References

[1] K. Ishihara, T. Yano, Org. Lett. 6 (2004) 1983–1986.
[2] A.E. Russell, S.P. Miller, J.P. Morken, J. Org. Chem. 65 (2000) 8381–8383.
[3] For reviews of Cu–bis(oxazoline) complexes in the asymmetric activation of carbonyls, see:
(a) J.S. Johnson, D.A. Evans, Acc. Chem. Res. 33 (2000) 325–335;
(b) K.A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, Acc. Chem. Res. 32 (1999) 605–613.
[4] J.W. Yang, B. List, Org. Lett. 8 (2006) 5633–5655.
[5] E. Aller, D.S. Brown, G.G. Cox, D.J. Miller, C.J. Moody, J. Org. Chem. 60 (1995) 4449–4460.