

Unusual chemoselective addition of diisopropylzinc to 2,2'-bipyridine-5,5'-dicarbonyl compounds in the 2-position and autoxidative reconversion with carbon–carbon bond cleavage

Shigehisa Tanji, Takanori Shibata, Itaru Sato and Kenso Soai*

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601 Japan. E-mail: ksoai@ch.kagu.sut.ac.jp

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Unusual chemoselective addition of diisopropylzinc to the 2-position of 2,2'-bipyridine-5,5'-dicarbonyl compounds affords the adducts with a quaternary carbon, and autoxidation of the adducts reconverts them into the initial compounds with carbon–carbon bond cleavage.

Synthetic utilities of organozinc reagents have dramatically increased during this decade.¹ The relatively mild nucleophilicity of dialkylzincs compared with alkyllithiums and Grignard reagents makes dialkylzincs more chemoselective reagents. For example, chiral amino alcohol catalysts enhance the nucleophilicity of dialkylzincs to add to aldehydes in an enantioselective manner.² On the other hand, addition of organometallic reagents to simple 2,2'-bipyridine normally occurs at the 6-position.^{3,4} To the best of our knowledge, the addition of organometallic reagents to the 2-position of 2,2'-bipyridine is very rare due to the steric hindrance of the 2-position.⁵ Meanwhile, the formation of the pyridine ring is hardly known by autoxidative carbon–carbon bond cleavage without using transition metals.⁶

We here report an unprecedented chemoselective addition of diisopropylzinc to the 2-position of 2,2'-bipyridine-5,5'-dicarbonyl compounds and the reconversion into the initial compounds with autoxidative carbon–carbon bond cleavage.

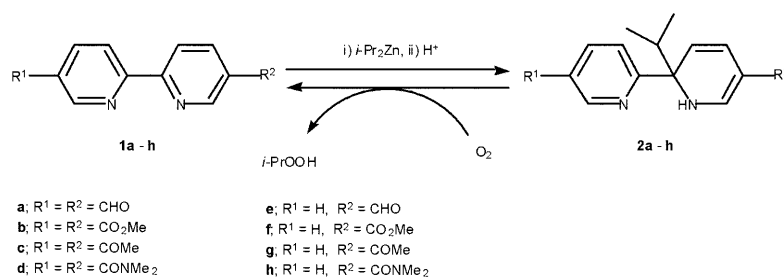
In the course of our study on asymmetric autocatalysis of 3-pyridylalkanol in the addition of diisopropylzinc (*i*-Pr₂Zn) to the aldehyde moiety of 5-carbamoylpyridine-3-carbaldehyde,⁷ we examined the reaction of *i*-Pr₂Zn with 2,2'-bipyridine-5,5'-dicarbonyl compounds (1a–h).⁸ Unexpectedly, *i*-Pr₂Zn (1.1 mol equiv.) did not add to the aldehyde moiety but to the 2-position of the bipyridine to afford 2a possessing a quaternary carbon atom in a yield of 69%.⁹ It should be emphasized that this chemoselectivity is quite unusual: the *i*-Pr₂Zn does not add to the aldehyde but to the 2-position of the bipyridine ring by destroying the aromaticity of the pyridine ring (Scheme 1).

We examined other organometallic reagents in the addition reaction to 1a at 0 °C. As shown in Table 1, isopropyl-

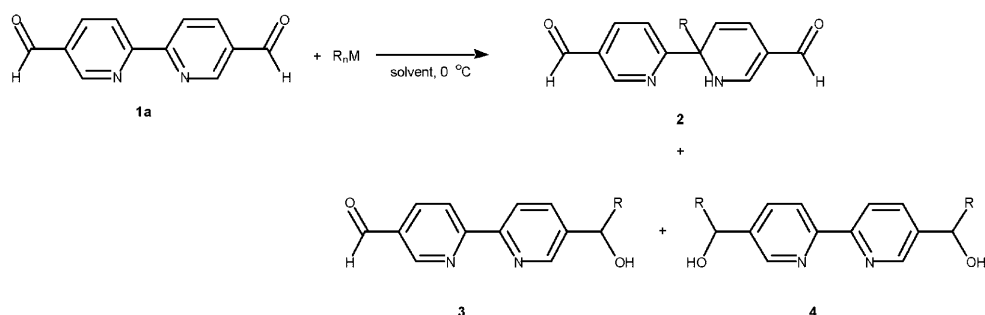
magnesium bromide did not add to bipyridine but exclusively added to the aldehyde to give the corresponding alkanol 3a and diol 4a in a total 52% yield (run 2). In the case of the addition using isopropylolithium, 2a was not formed. The reduction of aldehyde as a side reaction, was a major reaction, and alkanol 3a and diol 4a were obtained in low yields (run 3). Addition of diethylzinc and di(*n*-butyl)zinc occurred at the 2-position of 1a to give the corresponding adducts but in low yields along with the alkylated aldehyde products (runs 4 and 5). Thus, only *i*-Pr₂Zn gave 2a in a high yield by the chemoselective addition to the 2-position of 1a.

Generality of the addition of *i*-Pr₂Zn to the 2-positions of 2,2'-bipyridine-5,5'-dicarbonyl derivatives 1a–d is shown in Table 2.^{9,10} 2,2'-Bipyridine derivatives possessing two carbonyl substituents such as methoxycarbonyl, acetyl and dimethylcarbamoyl at the 5,5'-positions underwent the addition of *i*-Pr₂Zn to the 2-position to afford the adducts 2b–d in high yields of 88%, 93% and 82%, respectively (runs 2–4). Diisopropylzinc added to the 2-position of even 2,2'-bipyridine-5-carbonyl derivatives, possessing only one carbonyl substituent, to afford the corresponding adducts 2e–h in moderate yields (runs 5–8). On the other hand, in the cases of 2,2'-bipyridines (1i and 1j) without any carbonyl substituent at the 5,5'-positions, no alkylation occurred even at room temperature (runs 9 and 10). These results show that electron-withdrawing carbonyl substituent(s) at the 5- (and 5'-) position(s) activates bipyridine to undergo the addition of *i*-Pr₂Zn to the 2-position of 2,2'-bipyridine derivatives. This also explains the faster reactions with 1a–c possessing two carbonyl functionalities (1.1 mol equiv. of *i*-Pr₂Zn, 1 h) compared with 1e–g with one carbonyl functionality (3.0 mol equiv. of *i*-Pr₂Zn, 10–20 h).

When 6-phenylpyridine-3-carbaldehyde, without the 2,2'-bipyridine skeleton, reacted with *i*-Pr₂Zn in the presence of *N,N*-dibutylaminoethanol as a Lewis base, *i*-Pr₂Zn added only to the aldehyde moiety to afford pyridylalkanol in 60% yield. Thus, the structure of 2,2'-bipyridine is necessary for *i*-Pr₂Zn to add regioselectively to the 2-position. We think that the chelation by nitrogen atoms of bipyridine to the zinc atom



Scheme 1

Table 1 Nucleophilic addition of organometallic reagents to 2,2'-bipyridine-5,5'-dicarbaldehyde

Run	R _n M (equiv.)	Solvent	Yield of 2 (%)	Yield of 3 (%)	Yield of 4 (%)
1	<i>i</i> -Pr ₂ Zn (1.1)	Toluene	2a 69	3a 0	4a 0
2 ^a	<i>i</i> -PrMgBr (5.0)	THF–Et ₂ O	2a 0	3a 17	4a 35
3 ^{a,b}	<i>i</i> -PrLi (3.0)	Toluene–pentane	2a 0	3a 3	4a 9
4	Et ₂ Zn (5.0)	Toluene	19	18	24
5	<i>n</i> -Bu ₂ Zn (5.0)	Toluene	17	26	15

^a Reactions were carried out at rt. ^b Reduction of aldehyde to primary alcohol is a major reaction.

Table 2 Addition of diisopropylzinc to the 2-position of 2,2'-bipyridine derivatives

Run	2,2'-Bipyridine derivative 1	<i>i</i> -Pr ₂ Zn (equiv.)	Time/h	Yield of adduct 2 (%)
1 ^a	1a	1.1	1	2a 69
2 ^a	1b	1.1	1	2b 88
3 ^a	1c	1.1	1	2c 93
4 ^a	1d	5.0	48	2d 82
5 ^a	1e	3.0	10	2e 43
6 ^a	1f	3.0	20	2f 71
7 ^a	1g	3.0	12	2g 71
8 ^b	1h	5.0	48	2h 64
9 ^b	2,2'-Bipyridine 1i	3.0	24	0
10 ^b	5,5'-Dimethyl-2,2'-bipyridine 1j	3.0	24	0

^a Reactions were carried out at 0 °C. ^b Reactions were carried out at rt.

of *i*-Pr₂Zn has two effects: (1) it enhances the nucleophilicity¹¹ of *i*-Pr₂Zn, (2) it places *i*-Pr₂Zn near to the reaction site, *i.e.*, the 2-position of the 2,2'-bipyridine.

The adduct **2a** can be isolated and is stable under an argon atmosphere. We also found that, on exposure to the air at rt in dichloromethane, adduct **2a** converts into the initial 2,2'-bipyridine-5,5'-dicarbaldehyde **1a** in an almost quantitative yield (99%) (Scheme 1). In the NMR sample tube, we observed the formation of equimolar amounts of the initial **1a** and isopropyl hydroperoxide (confirmed by ¹H and ¹³C NMR and GLC analysis). The dealkylative autoxidation is probably due to the release of the steric congestion around the quaternary carbon atom (the 2-position) of **2a** and to the stabilization by aromatization. The addition of a radical initiator (AIBN) or UV irradiation in air accelerated the autoxidation. Conversely, autoxidation was suppressed by the addition of a radical scavenger such as 2,6-di-*tert*-butylphenol. Under the same conditions (air, CH₂Cl₂, rt, 1–7 d) adducts **2b–h** were easily converted into the corresponding initial 2,2'-bipyridines **1b–h** in high to quantitative (91% - quant.) yields.

As described, chemoselective addition of *i*-Pr₂Zn to the 2-position of 2,2'-bipyridine-5,5'-dicarbonyl compounds affords

unique adducts with quaternary carbons. Autoxidation of the adducts liberates the initial 2,2'-bipyridine-5,5'-dicarbonyl compounds and isopropyl hydroperoxide.

Notes and references

- Organozinc Reagents*, ed. P. Knochel and P. Jones, Oxford University Press, New York, 1999.
- K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833.
- T. Kauffmann, J. König and A. Woltermann, *Chem. Ber.*, 1976, **109**, 3864.
- Reviews on dihydropyridine: (a) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223; (b) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.
- For the addition of Grignard reagent to the 2-position of 2,2'-biquinolyl, S. Wakabayashi, Y. Kubo, T. Takeda, J. Uenishi and S. Oae, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2338.
- For the formation of a pyridine ring by carbon–carbon bond cleavage of 1,4-dihydropyridine using manganese dioxide, J. J. Vanden Eynde, F. Delfosse, A. Mayence and Y. van Haverbeke, *Tetrahedron*, 1995, **51**, 6511.
- (a) T. Shibata, H. Morioka, S. Tanji, T. Hayase, Y. Kodaka and K. Soai, *Tetrahedron Lett.*, 1996, **37**, 8783; (b) K. Soai, S. Niwa and H. Hori, *J. Chem. Soc., Chem. Commun.*, 1990, 982; (c) K. Soai, T. Shibata and I. Sato, *Acc. Chem. Res.*, 2000, **33**, 382.
- (a) J. de Mendoza, E. Mesa, J.-C. Rodriguez-Ubis, P. Vázquez, F. Vögtle, P.-M. Windscheif, K. Rissanen, J.-M. Lehn, D. Lilenbaum and R. Ziessel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1331; (b) F. Ebmeyer and F. Vögtle, *Chem. Ber.*, 1989, **122**, 1725.
- Satisfactory results were obtained from ¹H and ¹³C NMR, IR, high resolution mass spectra (HRMS) and/or elemental analyses for all new compounds.
- A typical experimental procedure is as follows (Table 1, run 1): a toluene solution of diisopropylzinc (1 M, 0.22 mL) was added dropwise to a stirred solution of dialdehyde **1a** (42.4 mg, 0.2 mmol) in toluene (7.0 mL) at 0 °C. After 1 h, the reaction was quenched by the addition of sat. aq. NaHCO₃ (10 mL) at 0 °C. The mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Purification of the residue by TLC on silica gel gave pure adduct **2a** as a colorless oil (35.4 mg) in 69% yield.
- (a) C. Bolm, M. Ewald and M. Felder, *Chem. Ber.*, 1992, **125**, 1205; (b) C. Bolm, M. Ewald, M. Felder and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169.