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An Improved Synthesis of Chiral 2,2′-Bipyridine Ligand C3-ACBP Without Column Chromatography

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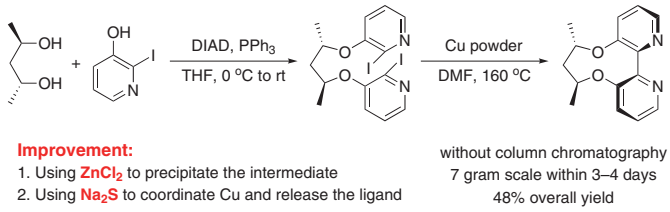

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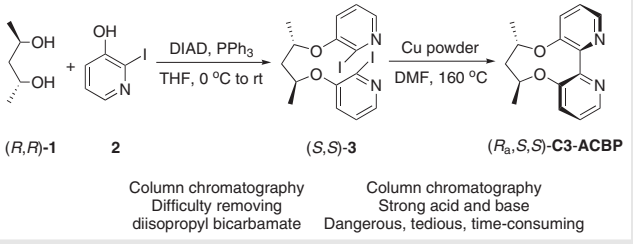
Abstract A method for purifying compounds bearing pyridine structure from Mitsunobu reaction mixtures using zinc chloride and releasing bipyridines from Ullmann coupling reaction mixtures by using sulfide anion for competitively coordinating the copper ion were developed for the facile synthesis of the chiral 2,2′-bipyridine ligand (R_a,*S*,*S*)-**C3-ACBP**. With these improvements, an improved synthesis of the chiral ligand at a 7 gram scale has been fulfilled in 48% overall yield without column chromatography within 3–4 days.

Key words 2,2′-bipyridine ligand, C3-ACBP, column chromatography free, zinc chloride, gram scale

The chiral bidentate *N*,*N*-ligands play an essential role in asymmetric catalysis and great progress has been achieved in their synthesis and applications in recent decades.[1] Compared with bis(oxazolines), diimines, bis(imidazolines), and other *N*,*N*-ligands, the development of the chiral 2,2′-bipyridine ligands is far behind, and only few of them are commercially available.[2] Among the reasons for such a situation, we think the synthesis of chiral 2,2′-bipyridine ligands may be one of the key factors. To prepare the chiral 2,2′-bipyridine ligands, chiral elements need to be introduced to the planar pyridine ring, and the chiral motif should be easily modular and tunable to balance stereocontrol and reactivity, which complicates their synthesis.[3b] The chiral 2,2′-bipyridine ligands with central,[3–7] planar,[8] or axial chirality[9,10] have been synthesized and applied for a variety of reactions, and some of them perform excellently. Among them, an axially chiral 2,2′-bipyridine ligand **C3-ACBP** has been developed and used in asymmetric C–H functionalization,[10] O–H insertion,[10a] arylation of *N*-tosylarylimines,[11] desymmetric C–O coupling,[12] diastereoselective C–C activation,[13] and so on;[14–16] and promising results have been achieved. Due to the relatively simple synthetic process of the **C3-ACBP** ligand and its encouraging performance in several types of reactions, we speculate that its applications in asymmetric catalysis will be extended, and its required amount will increase in the future. Thus, it is necessary to develop a more convenient synthetic process to obtain the **C3-ACBP** ligand at a large scale. Here we report an improved method based on the current synthetic process to synthesize the chiral **C3-ACBP** ligand in two steps at a 7 gram scale without column chromatography.

In the former reported procedures for the synthesis of (R_a,*S*,*S*)-**C3-ACBP** ligand,[10a] Mitsunobu reaction and Ullmann coupling reaction were respectively designed to afford the intermediate product (*S*,*S*)-**3** and the final product of (R_a,*S*,*S*)-**C3-ACBP** ligand starting from pentane-2,4-diol [(*R*,*R*)-**1**] and 2-iodopyridin-3-ol (**2**) (Scheme 1). In the first step of the Mitsunobu reaction, due to the use of an excess of diisopropyl azodicarboxylate and triphenylphosphine, a large amount of diisopropyl bicarbamate and triphenylphosphine oxide (TPPO) [over 4.0 equiv. to (*S*,*S*)-**3**] is produced as by-products, which makes the isolation of (*S*,*S*)-**3** from the reaction mixtures more difficult. Moreover, as diisopropyl bicarbamate has similar polarity to the target product (*S*,*S*)-**3**, it is awkward to remove it completely by recrystallization or column chromatography. In the second step of the Ullmann coupling reaction, due to the coordination between the (R_a,*S*,*S*)-**C3-ACBP** ligand and the copper ion, an excess amount of hydrochloric acid was used to dissociate the ligand from the copper and, at the same time, to form the hydrochloride salt of (R_a,*S*,*S*)-**C3-ACBP** ligand. To obtain the ligand, an excess amount of sodium hydroxide was added to precipitate the copper ion and neutralize the hydrochloride salt to release the free chiral bipyridine ligand. Such a manipulation process involving the intense exothermic neutralization of the strong acid and base is tedious and time-consuming. For both steps, column chromatography for the purification of the target products was

conducted, which is impractical and unsustainable for the synthesis of chiral intermediate (*S*,*S*)-**3** and the final bipyridine ligand at a large scale.



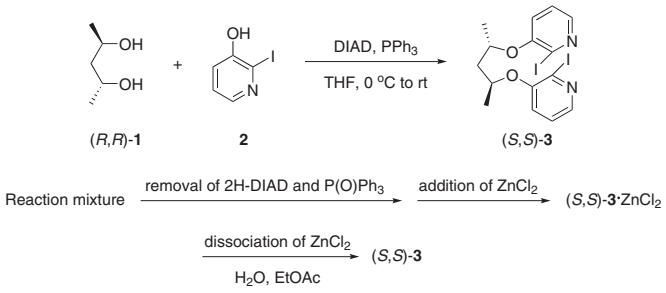
Scheme 1 The original synthetic method for chiral bipyridine ligand C3-ACBP

According to the limitations of the former procedures, we tried to improve the manipulation process of the first step with the aim of performing the reaction with (*R*,*R*)-**1** on a 100 mmol scale, producing over 50 grams of (*S*,*S*)-**3** theoretically. It has been reported that zinc chloride can precipitate TPPO in a polar solvent. In the presence of equivalent molar amounts of TPPO and 4-methoxypyridine, 4-methoxypyridine was also co-precipitated,[17] and 4-methoxypyridine is more easily precipitated by zinc chloride than TPPO as no 4-methoxypyridine was detected, while 4 percent of TPPO remained in the reaction solution after 22 hours. Considering that the desired product in the first step is (*S*,*S*)-**3** containing a pyridine structure, we anticipate that zinc chloride might first precipitate (*S*,*S*)-**3** if the conditions (solvent, reaction time, and temperature) are well controlled.

Actually, according to the literature, when warm ethanolic zinc chloride solution was added to the reaction mixture, no precipitate was formed, even after scraping to induce precipitation. Through several trials, we found that a white or light pink solid could be quickly formed in dichloromethane solution. After stirring or shaking for 30 minutes, the solid was collected by filtration. The dissociation of zinc chloride from the obtained solid was conducted by adding water and extracting with organic solvents. The obtained compound, after removing the organic solvents, was confirmed to be the target product (*S*,*S*)-**3** with a yield of 52%, which is pure enough for the next step. Although it is very convenient to get the pure intermediate (*S*,*S*)-**3** using this manipulation, such a yield is still unsatisfactory.

To further improve the yield, another part of zinc chloride was added to the filtrate to precipitate the (*S*,*S*)-**3** as much as possible using the same manipulation as above. However, the second time the obtained compound after dissociation of zinc chloride from the precipitate was confirmed to be a mixture of (*S*,*S*)-**3** and diisopropyl bicarbamate in a ratio of 1:2.4 as determined by ^{1}H NMR spectroscopy. This result implies that diisopropyl bicarbamate competitively coordinated with zinc chloride, and when its amount is far more than that of (*S*,*S*)-**3**, it will be co-precipitated with the (*S*,*S*)-**3** and zinc chloride. To avoid this situation, we tried to first get rid of the diisopropyl bicarbamate and TPPO. Fortunately, after evaporating the solvent tetrahydrofuran, through adding small amount of ethyl acetate and then suitable amount of petroleum ether to the residue, large amount of white solid precipitated from the solution, which was collected by filtration and confirmed to be a mixture of diisopropyl bicarbamate and TPPO. After removing most of the by-products of diisopropyl bicarbamate and TPPO, the following purification process of the desired product with zinc chloride proceeded smoothly, giving the pure (*S*,*S*)-**3** in 81% yield without containing diisopropyl bicarbamate or TPPO. Comparing the mass of precipitate before and after dissociating zinc chloride, the ratio of (*S*,*S*)-**3** to zinc chloride was calculated to be 1:1. Thus, the precipitated complex existed in the form of (*S*,*S*)-**3**·$ZnCl_2$ (Scheme 2).

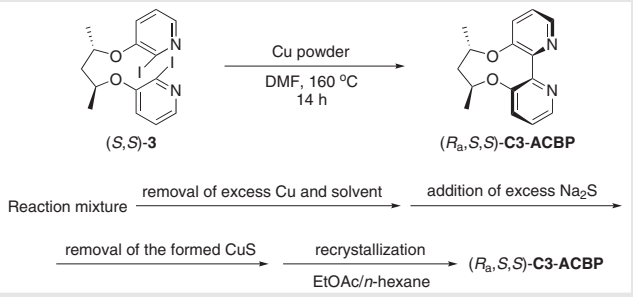
During this manipulation process, several points should be noted. One is regulating the amount of petroleum ether and ethyl acetate to precipitate the solid of diisopropyl bicarbamate and TPPO from the reaction mixture as much as possible. Too much ethyl acetate will dissolve the precipitate, and too much petroleum ether will make the solid sticky. The other is to use as little dichloromethane as possible to dissolve the residue, forming a homogeneous solution, and to wash the (*S*,*S*)-**3**·$ZnCl_2$ complex. Too much dichloromethane will dissolve the precipitate and reduce the isolated yield.



Scheme 2 The improved synthetic processing of step 1

In the second step of the reaction, due to the excess of copper ion coordinating with the target product (R_a,*S*,*S*)-**C3-ACBP** ligand, another reagent with stronger coordination ability to the copper ion than (R_a,*S*,*S*)-**C3-ACBP** ligand needs to be added to release the free ligand. The formerly reported method of using an excess of hydrochloric acid first and then sodium hydroxide to release the ligand is feasible, but it is not optimal. So, we tried to improve this process without using any strong acid and base.

As it is known that the precipitation equilibrium constant (K_{sp}) of copper sulfide (8.5×10^{-45}) is much smaller than that of copper hydroxide (2.2×10^{-20}), we anticipated that the sulfide anion, with a stronger coordination ability than the hydroxide anion, could possibly coordinate to the copper ion directly, forming the copper sulfide precipitate and releasing the free ligand. It is true that when we added excess solution of saturated sodium sulfide to the residue from which copper and solvent were removed, black precipitates formed. After removing the solid by filtration, the filtrate contained only the product and some black material that could be removed by recrystallization or filtration through a short silica gel column. Finally, the pure target product, chiral (R_a,*S*,*S*)-**C3-ACBP** ligand, could be obtained in a 59% isolated yield (Scheme 3).



Scheme 3 The improved synthetic processing step 2

In conclusion, we have developed the use of zinc chloride for purifying compounds bearing pyridine structures from Mitsunobu reaction mixtures and sulfide anion for competitively coordinating copper ions to release bipyridines from Ullmann coupling reaction mixtures for the synthesis of the (R_a,*S*,*S*)-**C3-ACBP** ligand. With these improvements, a simple and rapid synthesis of the ligand has been fulfilled at a 7 gram scale within 3-4 days without the need for column chromatography. This modified method provides the possibility for further amplification of this reaction and convenient workup of similar reactions.

Commercially available reagents were used without further purification. All solvents except DMF and THF, which were treated prior with 4Å molecular sieves were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at rt in $CDCl_3$ on 400 MHz instrument with TMS as internal standard. Optical rotations were measured by polarimeter. All reactions were monitored by TLC or NMR analysis.

3,3′-(2*S*,4*S*)-Pentane-2,4-diylbis(oxy)bis(2-iodopyridine) [(*S*,*S*)-3] [CAS Reg. No.: 1807966-66-0]

A solution of (2*R*,4*R*)-pentanediol [(*R*,*R*)-**1**; 10.42 g, 100 mmol), 2-iodopyridin-3-ol (**2**; 48.62 g, 220 mmol) and PPh_3 (62.95 g, 240 mmol) in anhyd THF (240 mL) in a 500 mL Schlenk flask was stirred at 0 °C for 10 min under N_2 atmosphere. To the above clear and highly vicious solution was added dropwise diisopropyl azodicarboxylate (50 mL, 240 mmol) within 60 min. Then, the reaction temperature was allowed to slowly warm up to rt and stirred for another 28 h. Then the solvent was evaporated to give a yellow semi-solid mixture. To this mixture, EtOAc (50 mL) was added to dissolve the semi-solid forming a homogeneous solution, followed by the addition of petroleum ether (250 mL). After shaking for a while, white solid precipitated and was filtered off. The solid was washed with a mixture of petroleum ether and EtOAc (*v*/*v* = 2:1, 3 × 60 mL). The collected filtrate was evaporated to give a yellow sticky residue, to which was added a warm solution of $ZnCl_2$ (27.26 g, 200 mmol) dissolved in absolute EtOH (200 mL) and then stirred or shaken for 15 min. The mixture was evaporated to give a viscous red liquid, which was then combined with as little CH_2Cl_2 as possible (?50 mL) until a homogeneous solution was formed. The solution was shaken or the bottle wall was scraped to induce precipitation until a pink precipitate was formed. The precipitate was filtered and washed with as less as possible of CH_2Cl_2 (4 × 20 mL) until the filtrate turned colorless. Then, to the pink precipitate was added H_2O (150 mL) and EtOAc (150 mL) and the mixture was stirred until the solid dissolved. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure to give (*S*,*S*)-**3** as a white or light yellow solid; yield: 41.22 g (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 4.6, 1.7 Hz, 1 H), 6.99 (dd, *J* = 8.2, 4.6 Hz, 1 H), 6.87 (dd, *J* = 8.3, 1.8 Hz, 1 H), 4.81–4.73 (m, 1 H), 2.12 (dd, *J* = 7.6, 5.4 Hz, 1 H), 1.41 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 142.6, 123.6, 119.3, 113.0, 72.9, 44.6, 20.1.

(R_a,*S*,*S*)-C3-ACBP

[CAS Reg. No.: 2770984-64-8]

To a stirred solution of 3,3′-(2*S*,4*S*)-pentane-2,4-diylbis(oxy)bis(2-iodopyridine) [(*S*,*S*)-**3**; 25.51 g, 50 mmol] in anhyd DMF (200 mL) was added activated Cu powder (31.77 g, 500 mmol) under N_2 atmosphere. The mixture was heated at 160 °C for 14 h. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to rt. The solid was filtered off with the Celite and washed with CH_2Cl_2 until the filtrate turned colorless. The solvent was evaporated under reduced pressure to give a black-brown residue. Then, excess of sat. aq Na_2S [over 5 equiv. to (*S*,*S*)-**3**] was added and the mixture was stirred for overnight. The solid was filtered off with Celite and washed with CH_2Cl_2 until the product cannot be detected by TLC in the fresh filtrate. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure to give the crude product as a black-brown solid, which could be further purified by recrystallization from EtOAc and *n*-hexane for 2–3 times to afford a white solid. The mother liquor was purified by silica gel filtration with a mixture of CH_2Cl_2 and MeOH (30:1). The filtrate was collected and evaporated to give a white solid product. The com-

bined chiral 2,2′-bipyridine ligand (R_a,*S*,*S*)-**C3-ACBP** was obtained as a white solid; yield: 7.56 g (59%); mp 215–216 °C; $[\alpha]_D^{20}$ –366.77 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (dd, *J* = 4.7, 1.4 Hz, 2 H), 7.43 (dd, *J* = 8.3, 1.4 Hz, 2 H), 7.30–7.27 (m, 2 H), 4.67–4.60 (m, 2 H), 1.96 (t, *J* = 4.2 Hz, 2 H), 1.43 (d, *J* = 6.5 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 149.4, 144.4, 124.8, 123.9, 75.6, 41.7, 22.6.

Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2063-1330.

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