Pd-catalyzed synthesis of 1-(hetero)aryl-2,2,2-trichloroethanols using chloral hydrate and (hetero)arylboroxines†

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1-(Hetero)aryl-2,2,2-trichloroethanols are useful key intermediates for the synthesis of various bioactive compounds. Herein, we describe N-heterocyclic carbene (NHC)-coordinated cyclometallated palladium complex (CYP)-catalyzed (hetero)aryl addition of chloral hydrate using (hetero)arylboroxines, providing a new approach to 1-(hetero)aryl-2,2,2-trichloroethanols. Notably, PhS-IPent-CYP which coordinated the bulky yet flexible 2,6-di(pentan-3-yl)aniline (IPent)-based NHC showed good catalytic activities and promoted the transformation in 24–97% yields.

Introduction

1-(Hetero)aryl-2,2,2-trichloroethanols are one of the most useful building blocks for the synthesis of bioactive compounds,1 because the carbinol moiety is easily transformed to various α-substituted carboxylic acid derivatives.2–4 So far, 1-(hetero)aryl-2,2,2-trichloroethanols have two kinds of possible synthetic routes as depicted in Scheme 1. One is an addition of the trichloromethyl anion to carbonyl compounds such as aldehydes or ketones (i).7 This way has generally needed the use of toxic trichloromethyl anion sources such as chloroform and trichloroacetic acid. The other is an addition of moisture-sensitive organometallic reagents such as organomagnesium compounds to dehydrated chloral (ii).8

The transition metal-catalyzed 1,2-addition of organoboron acids and their derivatives to carbonyl compounds is a convenient method compared to the Grignard reaction, which could be conducted in the presence of water.9 Although several research groups have reported the Rh-catalyzed 1,2-addition of arylboronic acids to trifluoromethyl ketones,10 the transition metal-catalyzed addition of arylboron compounds to trichloromethyl carbonyl compounds such as chloral have not been examined yet. It is well known that N-heterocyclic carbenes (NHC) coordinated palladium complexes are useful for various applications such as anticancer drugs, OLEDs and catalysts.11 Recently, we have developed the NHC coordinated cyclometallated palladium complexes (CYPs) that catalyzed the 1,2-addition of organoboron compounds to a wide range of carbonyl compounds including hemiacetals such as aqueous formaldehyde and glyoxylate hemiacetals (Scheme 2).12 Therefore, we envisaged that the NHC-CYPs exhibit a good catalytic activity of the addition of arylboron compounds to chloral hydrate without a dehydration process. Here, we report the direct aryl addition to chloral hydrate with triarylboroxines using NHC-CYPs as a catalyst.

Results and discussion

At first, we examined CYPs-catalyzed 1,2-addition of chloral hydrate 1 and 2-naphthylboron compounds (Table 1). PhS-IPr-CYP have catalyzed the addition of arylboronic acids to an excess amount of aqueous formaldehyde to provide the corresponding benzyl alcohols in satisfactory yields,12a,d although PhS-IPr-CYP catalyzed reaction of 2-

Scheme 1 Previous synthesis of trichloromethylcarbinols.
Naphthaleneboronic acid 2a and 4 equivalent of chloral hydrate afforded the desired product 5a in 39% yield (entry 1). In this case, the yield of 5a was improved by the use of an excess of 2a relative to chloral hydrate (entry 2). Then, using 2-naphthaleneboronate 3a instead of 2a increased slightly the yield of 3a to 70% (entry 3). We have confirmed the efficacy of arylboroxines in the arylation of trifluoroacetaldehyde hemiacetal from a preliminary investigation. When this reaction was performed using tri(naphthalene-2-yl)boroxine 4a, the yield of 5a was improved considerably to 82% (entry 4). Dehydrated chloral was usable as well as chloral hydrate for this addition reaction (entry 5).

H-IPr-CYP has shown more catalytic activity than PhS-IPr-CYP in the CYPs-catalyzed arylation of glyoxylate hemiacetals, but it was not suitable for this reaction (entry 6). PhS-IPent-CYP having sterically bulky alkyl group had more active towards the addition than PhS-IPr-CYP (entry 7).

Under the optimized conditions, we synthesized various functionalized trichloromethyl carbinols using PhS-IPent-CYP catalyzed reaction (Table 2). Substrates bearing sterically hindered 1-naphthyl group was also converted to the corresponding alcohol 5b in moderate yield of 65%. Arylboroxines bearing electron-donating groups like tert-butyl, phenyl, methoxy and methylthio groups furnished the corresponding products 5c–5h in satisfactory yields of 66–97%. Interestingly, sterically bulky 2-methoxyphenylboroxine reacted more smoothly than 3-methoxyphenyl and 4-methoxyphenylboroxines. 4-Fluorophenyl and 4-bromophenylboroxines provided the corresponding products 5i and 5j in excellent yields, but the reaction using aryloboroxines having strong electron-withdrawing groups such as nitrile, nitro or methoxycarbonyl group have not afforded the products 5k–5m. Remarkably, the bromo group on the aromatic ring remained intact, and the Suzuki–Miyaura cross-coupling product did not observe under this reaction condition. This catalytic reaction was also applicable to heteroarylboroxines containing oxygen or sulfur atom and provided the products 5n–5r in low to moderate yields, but was not applicable to an aliphatic boroxine such as 2-phenylethylboroxine 4s.

Since aryloboroxines are more suitable for this reaction than aryloboric acids, we examined an experiment under the reaction conditions with H2O (Scheme 3). Because aryloboroxines is known to rapidly absorb H2O and transform to boronic acids, and adding water is expected to reduce the dehydration performance of boroxine. Practically, the yield declined as the amount of H2O added increased, indicating that aryloboroxines may be involved in the dehydration step of chloral hydrate. So, we proposed a plausible catalytic cycle which is described in Scheme 4. Initially, dehydrated chloral and arylboronic acids are generated from the hydrolysis of aryloboroxines by chloral hydrate. Then arylpalladium intermediate 6 is formed from a base-promoted transmetallation between an arylboronic acid and PhS-IPent-CYP, alkoxypalladium 7 is generated from an insertion of the aryl group on 6 to chloral. Finally, a transmetallation of complex 7 between an arylboronic acid

Table 1 Optimization of reaction conditions of CYPs-catalyzed 1,2-addition of chloral hydrate 1 and 2-naphtalenelboron compounds

| Entry | 1 (mmol) | B (mmol) | K2CO3 (mmol) | CYPs | Yielda (%) |
|-------|----------|----------|--------------|------|------------|
| 1     | 2.0      | 0.5      | 0.5          | PhS-IPr-CYP | 39         |
| 2     | 0.5      | 1.5      | 1.5          | PhS-IPr-CYP | 66         |
| 3b    | 0.5      | 1.5      | 1.5          | PhS-IPr-CYP | 70         |
| 4c    | 0.5      | 0.5      | 1.5          | PhS-IPr-CYP | 82         |
| 5da   | 0.5      | 0.5      | 1.5          | PhS-IPent-CYP | 81       |
| 6d    | 0.5      | 0.5      | 1.5          | H-IPr-CYP  | 73         |
| 7e    | 0.5      | 0.5      | 1.5          | PhS-IPent-CYP | 95 (95)   |

Yields were determined by 1H-NMR using triphenylmethane as an internal standard. 3a was used instead of 2a. 4a was used instead of 2a. Dehydrated chloral was used instead of chloral hydrate. Isolated yield.
results in the formation of 1-(hetero)aryl-2,2,2-trichloroethanol and the regeneration of complex 6.

Conclusions

We have achieved a nucleophilic arylation to chloral hydrate using PhS-IPent-CYP as a catalyst. The use of arylboroxine is critical for this reaction, and arylboroxines have acted not only as an arylcarbanion source but also as a dehydrating agent for chloral hydrate.

Experimental

General

All reactions were carried out under an argon atmosphere. $^1$H, $^{13}$C, and $^{19}$F NMR spectra were recorded on an AVANCE III 400 spectrometer (400.15 MHz) at ambient temperature. Melting points were recorded on Yanako MP-S3. HRMS were recorded on a Thermo Fisher Scientific Exactive (Orbitrap) using ESI or APCI. Commercially available organic and inorganic compounds were used without purification. PhS-IPr-CYP, $^{12}$a H-IPr-CYP, $^{12}$a PhS-IPent-CYP $^{12}$d and arylboroxines $^{413}$ were prepared according to the literature procedures.

Preparation and characterizations of compounds

2,2,2-Trichloro-1-(naphtalen-2-yl)ethan-1-ol $^{7b}$ 5a. Chloral hydrate (83 mg, 0.50 mmol), 2-naphtyl boroxine (231 mg, 0.500 mmol), PhS-IPent-CYP (6.1 mg, 0.0050 mmol) and potassium carbonate (207 mg, 1.50 mmol) were charged in 10 mL test tube sealed with a rubber septum. The test tube was evacuated and backfilled with argon. This sequence was repeated three times. Then dehydrated toluene (1 mL) was added via the rubber septum with syringe. In an argon flow, the rubber septum was replaced with a Teflon liner screw cap. The sealed test tube was placed into an oil bath preheated 100–140°C. After the reaction was stirred for 2 h and cooled to room temperature, the obtained crude was purified by passing it through a silica gel column with a hexane/ethyl acetate to give 131 mg (0.475 mmol, 95%) of product $^{5a}$ as a pale yellow solid, mp 93–94°C (lit. $^{7b}$ 93–94°C).

$^1$H NMR (400 MHz, CDCl$_3$, ppm): δ 8.09 (s, 1H, ArH), 7.85–7.90 (m, 3H, ArH), 7.88 (dd, J$_1$ = 7.3 Hz, J$_2$ = 9.8 Hz, 1H, ArH), 7.52 (t, J = 4.1 Hz, 2H, ArH), 5.40 (d, J = 3.4 Hz, 1H, CH(OH)CCl$_3$), 3.39 (d, J = 3.4 Hz, 1H, OH)$_2$; $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): δ 133.8 (Ar), 132.5 (Ar), 132.3 (Ar), 129.3 (Ar), 128.4 (Ar), 127.7 (Ar), 127.4 (Ar), 126.9 (Ar), 126.4 (Ar), 126.2 (Ar), 103.3 (CCl$_3$), 84.7 (CH(OH)CCl$_3$); HRMS (EI) m/z: [M + Cl]$^-$ calefd for C$_{12}$H$_9$OCL$_4$: 308.9413. Found: 308.9424.
2,2,2-Trichloro-1-(naphthalen-1-yl)ethan-1-ol<sup>5b</sup> 5b. Product 5b was prepared by utilizing the general procedure using 1-naphthyl boroxine (231 mg, 0.500 mmol) and was isolated as a pale yellow liquid (91 mg, 0.43 mmol, 66%).<sup>1</sup> H NMR (400 MHz, CDCl<sub>3</sub>, ppm): δ 8.28 (d, J = 8.5 Hz, 1H, ArH), 8.09 (d, J = 8.5 Hz, 1H, ArH), 7.91–7.97 (m, 2H, ArH), 7.51–7.62 (m, 3H, ArH), 6.23 (d, J = 4.2 Hz, 1H, CH(OH)CCl<sub>3</sub>), 3.45 (d, J = 4.2 Hz, 1H, OH);<sup>1</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm): δ 133.5 (Ar), 132.0 (Ar), 131.4 (Ar), 130.3 (Ar), 129.0 (Ar), 127.2 (Ar), 126.4 (Ar), 125.6 (Ar), 124.9 (Ar), 123.7 (Ar), 103.5 (CCl<sub>3</sub>), 79.0 (CH(OH)CCl<sub>3</sub>); HRMS (EI) m/z: [M + Cl]<sup>+</sup> c...
liquid (68 mg, 0.29 mmol, 59%). $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.55 ($t, J = 2.4$ Hz, 1H, ArH), 7.32 ($m, 2H, ArH$), 5.32 ($d, J = 4.4$ Hz, 1H, CH(OH)Cl$_3$), 3.29 ($d, J = 4.4$ Hz, 1H, CCl$_3$); $^1$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 136.0 (Ar), 127.6 (Ar), 126.2 (Ar), 125.2 (Ar), 102.8 (CCl$_3$), 81.3 (CH(OH)Cl$_3$); HRMS (EI) $m/z$: [M + Cl]$^-$ calecd for C$_{10}$H$_7$OCl$_3$: 298.9206. Found: 298.9216.

2,2,2-Trichloro-1-(furan-3-yl)ethan-1-ol 5p. Product 5p was prepared by utilizing the general procedure using 3-furan boronic acid (141 mg, 0.500 mmol) and was isolated as a pale yellow solid (80 mg, 0.30 mmol, 60%), mp 71

Acknowledgements

We thank Prof. Mino, Chiba University, for the HRMS measurements. This work was supported in part by the Research Institute for Science and Technology, Tokyo Denki University Grant Number Q19E-06 and Q18E-04.

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