Allylic cross-coupling using aromatic aldehydes as α-alkoxyalkyl anions

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Abstract

The allylic cross-coupling using aromatic aldehydes as α-alkoxyalkyl anions is described. The synergistic palladium/copper-catalyzed reaction of aromatic aldehydes, allylic carbonates, and a silylboronate produces the corresponding homoallylic alcohol derivatives. This process involves the catalytic formation of a nucleophilic α-silyloxybenzylcopper(I) species and the subsequent palladium-catalyzed allylic substitution.

Introduction

α-Alkoxy-substituted carbanions (α-alkoxyalkyl anions) are useful C(sp^3) nucleophiles for the construction of alcohol units found in a majority of pharmaceuticals, agrochemicals and bioactive natural products. Generally, α-alkoxyalkyl anions are presynthesized as stoichiometric organometallic reagents such as organolithium, organozinc, organocuprate, organostannane, organosilane and organoboron compounds [1-6]. Alternatively, we showed that easily available aromatic aldehydes can be used as α-alkoxyalkyl anions for catalytic carbon–carbon bond formations [7-9]. For example, a nucleophilic α-silyloxybenzylcopper(I) species can be generated catalytically from aromatic aldehydes through the 1,2-addition of a silylcopper(I) species

followed by [1,2]-Brook rearrangement and then successfully trapped with aryl bromides under palladium catalysis (Scheme 1). This system was extended to an asymmetric version using the chiral α-silyloxybenzylcopper(I) species having a chiral NHC ligand. In the asymmetric system, one example of allylic carbonate was used as the carbon electrophile [8,10,11]. This paper describes in full detail the racemic system using allylic carbonates. The allylic cross-coupling of aromatic aldehydes and allylic carbonates with a silylboronate by the merging of a copper–*N*-heterocyclic carbene catalyst and a palladium–bisphosphine catalyst produced homoallylic alcohol derivatives [12-14].

Scheme 1: Our strategy.

Results and Discussion

Specifically, the three-component allylic cross-coupling reaction of benzaldehyde (**1a**, 0.4 mmol), *tert*-butyl cinnamyl carbonate (**2a**, 0.2 mmol) and (dimethylphenylsilyl)boronic acid pinacol ester [PhMe$_2$SiB(pin)] (0.4 mmol) occurred in the presence of catalytic amounts of Pd(OCOCF$_3$)$_2$ (3 mol %), DPPF (3 mol %), (SIPr)CuCl (15 mol %) and KO*t*-Bu (25 mol %) in toluene at 80 °C to afford homoallylic alcohol derivative **3aa** in 64% yield (based on **2a**) (Scheme 2). The reaction yielded small amounts of side products such as cinnamylsilane and benzyl silyl ether, which are derived from the Pd-catalyzed allylic silylation of **2a** and the Cu-catalyzed silylation of **1a** and the subsequent [1,2]-Brook rearrangement, respectively. In this coupling reaction, (SIPr)CuCl was a slightly better copper complex than (IPr)CuCl (62%), (SIMes)CuCl (60%) and (IMes)CuCl (53%) in terms of the chemical yield. Notably, the allylic cross-coupling reaction did not occur at all without Pd(OCOCF$_3$)$_2$–DPPF or (SIPr)CuCl, and thus the palladium and copper catalysts cooperatively acted in the allylic cross-coupling.

Scheme 3 shows the substrate range of aromatic aldehydes **1** and allylic carbonates **2**. Methyl, *tert*-butyl and fluoro substituents were tolerated at the *ortho*- or *para*-positions of the aromatic aldehyde (**3ba–da**). 2,6-Dimethylphenyl- or 1-naphthyl moieties as the γ-substituent of the primary allylic carbonate were tolerated in the reaction (**3ab** and **3ac**). Cinnamyl carbonates having a fluoro or acetal substituent were also suitable coupling partners (**3ad** and **3ae**).

The synergistic palladium/copper catalysis was used for the reaction of a secondary allylic carbonate. For example, the allylic cross-coupling of **2a'**, a constitutional isomer of **2a**, with benzaldehyde (**1a**) afforded the linear allylation product **3aa** with complete regioselectivity. The symmetric secondary allylic carbonate was converted to the corresponding homoallylic alcohol derivative in 50% yield (**3af**).

To gain understanding into the mechanism of this synergistic palladium/copper-catalyzed allylic cross-coupling, a stoichiometric experiment was conducted (Scheme 4). The reaction of the SIPr-ligated α-silyloxybenzylcopper **4** with the cinnamyl–palladium complex **5**, which was prepared in situ from [(cinnamyl)PdCl]$_2$ and DPPF, gave the corresponding homoallylic alcohol derivative **3aa**.

Based on previous reports and the outcome obtained by the stoichiometric experiment in Scheme 4, a possible reaction pathway involving a cooperative action of palladium and copper catalysis can be proposed as illustrated in Scheme 5. The reaction of SIPr-ligated CuCl (**A**), KO*t*-Bu and a silylboronate produces a silylcopper(I) species **B**. The 1,2-addition of silylcopper(I) **B** to the aromatic aldehyde **1** [15-19] and the subsequent [1,2]-Brook rearrangement from the obtained α-silyl-substituted copper(I) alkoxide **C** forms the key intermediate, an α-silyloxybenzylcopper(I) species **D**. The transmetalation between **D** and an allylpalladium(II) species **F** that is generated through the oxidative addition of an allylic carbonate **2** across a palladium(0)–DPPF complex **E**, followed by
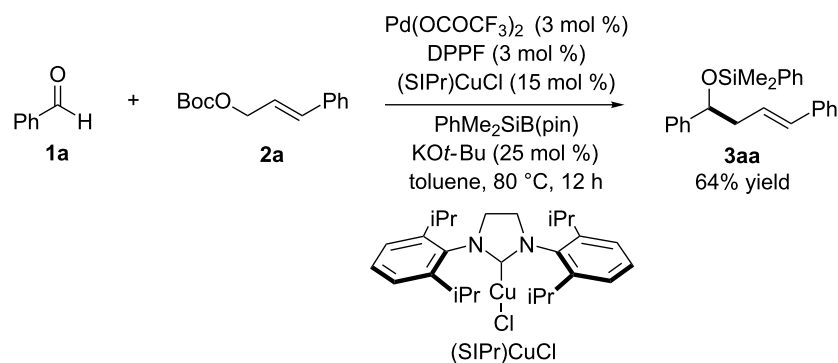

Scheme 2: Allylic cross-coupling using aldehydes as α-alkoxyalkyl anions.
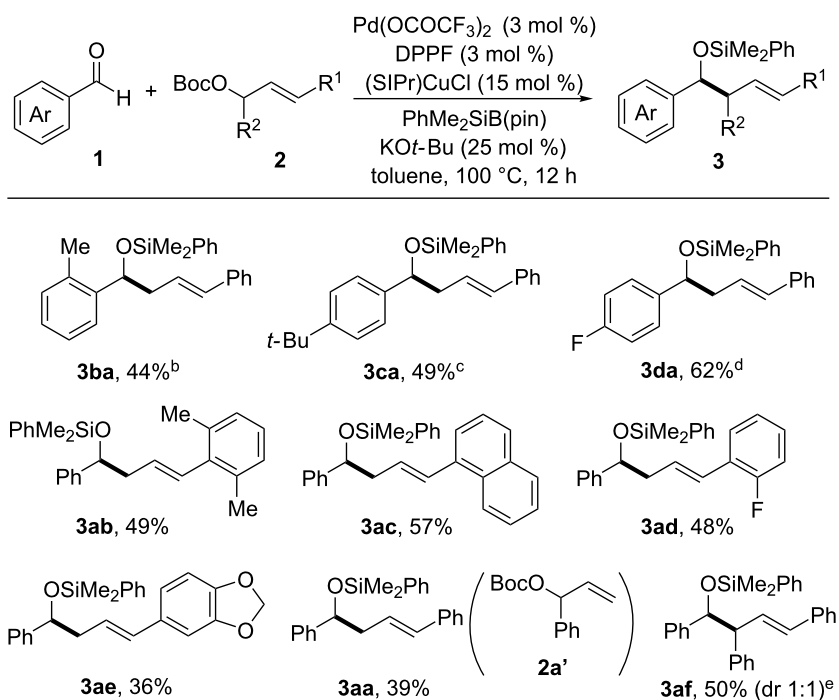
Scheme 3: Substrate scope and reaction conditions. a) reactions were carried out with **1** (0.4 mmol), **2** (0.2 mmol), PhMe$_2$SiBpin (0.4 mmol), Pd(OCOCF$_3$)$_2$ (3 mol %), DPPF (3 mol %), (SIPr)CuCl (15 mol %), KO*t*-Bu (25 mol %) in toluene (2 mL) at 100 °C for 12 h. b) Pd(OCOCF$_3$)$_2$/DPPF (3 mol %), (SIPr)CuCl (25 mol %) and KO*t*-Bu (35 mol %) were used and the reaction temperature was decreased to 80 °C. c) Pd(OCOCF$_3$)$_2$/DPPF (3 mol %), (SIPr)CuCl (25 mol %) and KO*t*-Bu (35 mol %) were used. d) The reaction temperature was decreased to 80 °C. e) Pd(OCOCF$_3$)$_2$/DPPF (5 mol %), (SIPr)CuCl (25 mol %) and KO*t*-Bu (35 mol %) were used.
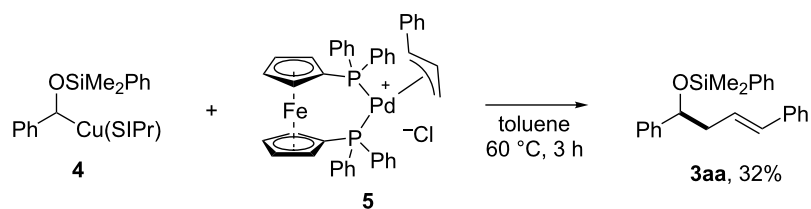
Scheme 4: Stoichiometric reaction.
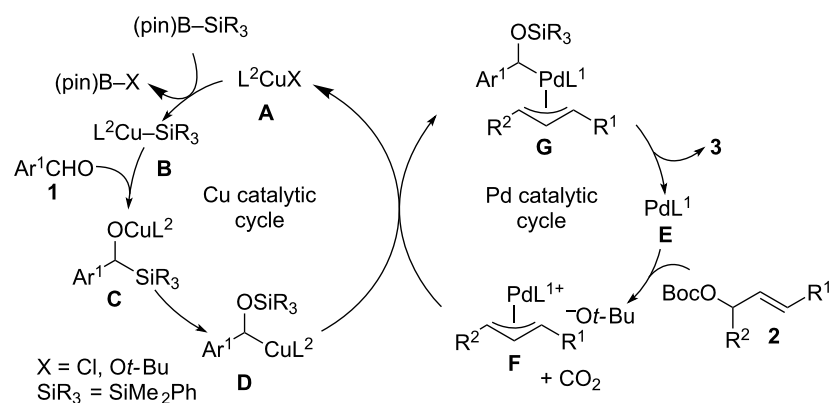
Scheme 5: Possible pathway.

reductive elimination from **G** produces the homoallylic alcohol **3** and then regenerate **A** and **E** for the next catalytic cycle [20-23].

Conclusion

In summary, we developed an umpolung strategy for catalytically formed α-alkoxyalkyl anions from aromatic aldehydes for the use in allylic cross-coupling reactions. The synergistic palladium/copper-catalyzed reaction of aromatic aldehydes, allylic carbonates, and a silylboronate delivered the homoallylic alcohol derivatives. This process involves the catalytic formation of a nucleophilic α-silyloxybenzylcopper(I) species and the subsequent palladium-catalyzed allylic substitution.

Experimental

SIPrCuCl (14.7 mg, 0.03 mmol), and KO*t*-Bu (4.5 mg, 0.04 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon®-coated silicon rubber septum, and then the vial was evacuated and filled with nitrogen. Toluene (0.6 mL) was added to the vial, and then the mixture was stirred at 25 °C for 10 min. Next, PhMe$_2$SiB(pin) (104.9 mg, 0.4 mmol) and benzaldehyde (**1a**, 42.4 mg, 0.4 mmol) were added, and the mixture (mixture A) was stirred at 25 °C for 10 min. Meanwhile, Pd(OCOCF$_3$)$_2$ (2.0 mg, 0.006 mmol) and DPPF (3.3 mg, 0.006 mmol) were placed in another vial. This vial was sealed with a Teflon®-coated silicon rubber septum and then evacuated and filled with nitrogen. After toluene (0.8 mL) was added to the vial, the mixture was stirred at 25 °C for 10 min. Next, KO*t*-Bu (1.1 mg, 0.01 mmol) and allylic carbonate **2a** (46.9 mg, 0.2 mmol) were added to the vial, and the mixture (mixture B) was stirred at 25 °C for 10 min. Finally, the palladium solution (mixture B) was transferred to the vial (mixture A) containing the copper complex with toluene (0.6 mL). After 12 h stirring at 80 °C, the reaction mixture was diluted with diethyl ether (1 mL). The reaction mixture was filtered through a short plug of aluminum oxide (1 g) with diethyl ether as an eluent. After volatiles were removed under reduced pressure, GPC (EtOAc) followed by flash chromatography on silica gel (0–1% EtOAc/hexane) gave product **3aa** in 64% isolated yield (45.7 mg, 0.13 mmol).

Supporting Information

Supporting Information File 1
Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra for newly synthesized compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-21-S1.pdf]

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References

1. Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 2282–2316. doi:10.1002/anie.199722821
2. Still, W. C. *J. Am. Chem. Soc.* **1978,** *100,* 1481–1487. doi:10.1021/ja00473a025
3. Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2002,** *4,* 119–122. doi:10.1021/ol016986e
4. Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron Lett.* **1987,** *28,* 3911–3914. doi:10.1016/s0040-4039(00)96418-9
5. Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2008,** *47,* 1770–1773. doi:10.1002/anie.200704696
6. Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006,** *128,* 11036–11037. doi:10.1021/ja064019z
7. Takeda, M.; Yabushita, K.; Yasuda, S.; Ohmiya, H. *Chem. Commun.* **2018,** *54,* 6776–6779. doi:10.1039/c8cc01055b
8. Yabushita, K.; Yuasa, A.; Nagao, K.; Ohmiya, H. *J. Am. Chem. Soc.* **2019,** *141,* 113–117. doi:10.1021/jacs.8b11495
9. Takeda, M.; Mitsui, A.; Nagao, K.; Ohmiya, H. *J. Am. Chem. Soc.* **2019,** *141,* 3664–3669. doi:10.1021/jacs.8b13309
10. Nahra, F.; Macé, Y.; Lambin, D.; Riant, O. *Angew. Chem., Int. Ed.* **2013,** *52,* 3208–3212. doi:10.1002/anie.201208612
11. Jia, T.; Cao, P.; Wang, B.; Lou, Y.; Yin, X.; Wang, M.; Liao, J. *J. Am. Chem. Soc.* **2015,** *137,* 13760–13763. doi:10.1021/jacs.5b09146
12. Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008,** *130,* 6340–6341. doi:10.1021/ja802001b
13. Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014,** *53,* 9142–9150. doi:10.1002/anie.201403873
14. Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014,** *79,* 5970–5986. doi:10.1021/jo501004j
15. Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. – Eur. J.* **2011,** *17,* 13538–13543. doi:10.1002/chem.201102367
16. Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Díaz Álvarez, J.; Robeyns, K.; Riant, O. *Angew. Chem., Int. Ed.* **2013,** *52,* 1785–1788. doi:10.1002/anie.201209020
17. Delvos, L. B.; Hensel, A.; Oestreich, M. *Synthesis* **2014,** *46,* 2957–2964. doi:10.1055/s-0034-1378542
18. Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013,** *113,* 402–441. doi:10.1021/cr3003517
19. Hensel, A.; Oestreich, M. Asymmetric Addition of Boron and Silicon Nucleophiles. In *Progress in Enantioselective Cu(I)-catalyzed Formation of Stereogenic Centers;* Harutyunyan, S., Ed.; Top. Organomet. Chem., Vol. 58; Springer: Cham, Switzerland, 2016; pp 135–167. doi:10.1007/3418_2015_156
20. Pye, D. R.; Mankad, N. P. *Chem. Sci.* **2017,** *8,* 1705–1718. doi:10.1039/c6sc05556g

21. Semba, K.; Nakao, Y. *J. Am. Chem. Soc.* **2014,** *136,* 7567–7570.
doi:10.1021/ja5029556

22. Smith, K. B.; Logan, K. M.; You, W.; Brown, M. K. *Chem. – Eur. J.*
2014, *20,* 12032–12036. doi:10.1002/chem.201404310

23. Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016,**
138, 8372–8375. doi:10.1021/jacs.6b04566

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