Copper-Catalyzed Borylative Aromatization of \( p \)-Quinone Methides: Enantioselective Synthesis of Dibenzylic Boronates

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Supporting Information

ABSTRACT: In this report, we establish that DM-Segphos copper(I) complexes are efficient catalysts for the enantioselective borylation of \( p \)-quinone methides. This method provides straightforward access to chiral monobenzylic and dibenzylic boronic esters, with enantiomeric ratios up to 96:4, using a commercially available chiral phosphine. Standard manipulations of the C–B bond afford a variety of chiral diaryl derivatives.

KEYWORDS: asymmetric catalysis, boron, copper, synthetic methods, asymmetric synthesis

Chiral secondary boronic esters are important intermediates in organic synthesis, because they are precursors of chiral alcohols, chiral amines, and tertiary stereocenters. Among them, dibenzylic boronates such as B are especially interesting, because they can provide a variety of enantiomerically enriched diaryl derivatives (see Scheme 1). The diarylmethane framework represents a privileged structural motif widely found in pharmaceuticals. Most of these biologically active compounds present a chiral center at the benzyl position with a stereodefined C–O, C–N, or C–C bond. We envisioned that functionalization of the C–B bond in B could offer a unified strategy for the preparation of these compounds, from a common intermediate. However, the enantioselective synthesis of dibenzylic boronic esters is still a difficult challenge in chemical synthesis.

At the outset of this project, the only method available for the synthesis of boronates such as B involved the use of chiral lithiated carbamates and aryl boronic esters (Scheme 1). Despite the undoubted significance of this approach, the yields were moderate, and a stoichiometric amount of a chiral ligand was required. As part of our interest in unconventional C–B bond formation, we envisioned a new approach toward the synthesis of dibenzylic boronates through the enantioselective 1,6-addition of a chiral copper-(I) boryl complex to a \( p \)-quinone methide (Scheme 1). Formally, \( p \)-quinone methides are neutral entities with a zwitterionic resonance structure that enhances the electrophilic character at the \( \delta \)-position. Surprisingly, while ortho-quinone methides have been broadly used in asymmetric synthesis, only two catalytic enantioselective additions to \( p \)-quinone methides have been reported. Both methods use carbon-based nucleophiles and an organocatalyst to control the enantioselectivity. Therefore, we became intrigued in exploring these compounds for several reasons:

1. the use of asymmetric metal catalysis to functionalize \( p \)-quinone methides remained unexplored;

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(2) the introduction of a boronic ester unit in ortho- or para-quione methide had not been reported; and
(3) the stereoselective addition of heteroatomic nucleophiles to p-quione methides had not been studied to date.

Herein, we describe the synthesis of dibenzylic boronates through the borylative aromatization of p-quione methides with high yields and high enantioselective values, under mild reaction conditions and using a commercially available chiral phosphine.9,10

While unsubstituted p-quione methides (R2, R3 = H) are too reactive to be isolated, 2,6-disubstituted derivatives are easy to handle. We began our study with p-quione methide 1a, which contains removable t-Bu groups at the α-positions (Table 1).11 When 1a was treated in THF with Cu(CH3CN)4PF6 (5 mol %), L2 (10 mol %), B2pin2 (1.5 equiv), NaOMe (4 equiv) for 2 h, the desired dibenzylic boronate 2a was obtained in 35% yield. The reaction conditions were further optimized with the use of chiral sulfoxide-phosphine ligands (Table 2).

Table 1. Effect of the Chiral Ligand in the Borylative Aromatization of p-Quione Methides[a]

| entry | L[a] | enantiomeric ratio, er[^b] | yield (%)[^c] |
|-------|------|---------------------------|--------------|
| 1[^a] | L1   | 54.5:45.5                 | 35           |
| 2[^a] | L1   | 65:35                     | 47           |
| 3[^a] | L2   | 77:23                     | 76           |
| 4[^a] | L3   | 83:17                     | 68           |
| 5[^a] | L4   | 66.5:33.5                 | 41           |
| 6[^a] | L5   | 96:4                      | 95           |
| 7[^a] | L6   | 94:6                      | 79           |
| 8[^d] | L6   | 74:26                     | 54           |

[a]Reaction conditions: 1 (0.2 mmol), B2pin2 (0.30 mmol), NaOMe-Bu (20 mol %), Cu(CH3CN)4PF6 (10 mol %), L1 (11 mol %), MeOH (0.8 mmol), THF (0.2 M).[^b]er determined by chiral SFC.[^c]Yield of isolated 2.[^d]Reaction conditions: 1 (0.2 mmol), B2pin2 (0.30 mmol), NaOMe-Bu (20 mol %), Cu(CH3CN)4PF6 (5 mol %), L2 (5.5 mol %), MeOH (0.8 mmol), THF (0.2 M). The reaction was carried out in the absence of MeOH.

(2) the introduction of a boronic ester unit in ortho- or para-quione methide had not been reported; and
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methide 1i (R² = Me, R¹ = Ph) as models. Noteworthy, no simplification of the ligand structure was used in order to properly consider the steric effects around the metal center. As shown in Scheme 4, the boryl cupration is a highly exergonic and, therefore, irreversible process. Since the absolute configuration of the new stereogenic carbon is fixed in this step, enantioselectivity is kinetically controlled. Transition states for the boryl cupration (TS_R and TS_S) were located and allowed the calculation of the corresponding activation energies for the formation of both enantiomers. The free energy of TS_S is 0.9 kcal mol⁻¹ lower than that corresponding to TS_R, because of better substrate accommodation within the

Scheme 2. Borylative Aromatization of Nonsymmetric p-Quinone Methides

Scheme 3. C–B Bond Functionalization

Table 2. Substrate Scope

| R¹ | R² | Yield | ee (%) |
|----|----|-------|--------|
| H  | Me | 2a    | 95%    | 96.4   |
| Br | Me | 2b    | 78%    | 96.4   |
| H  | Ph | 2c    | 63%    | 93.7   |
| H  | Me | 2d    | 77%    | 93.7   |
| Br | Me | 2e    | 79%    | 94.0   |
| Br | Ph | 2f    | 84%    | 90.4   |
| Br | Me | 2g    | 69%    | 90.4   |
| Br | Ph | 2h    | 76%    | 93.7   |
| Me | H  | 3a    | 65%    | 96.0   |
| Me | Ph | 3b    | 95%    | 96.4   |
| Me | Me | 3c    | 71%    | 95.5   |
| Br | Me | 4a    | 63%    | 95.5   |
| Br | Ph | 4b    | 71%    | 96.0   |
| Br | Br | 4c    | 63%    | 95.5   |

[a] Reaction conditions: 1 (0.2 mmol), B₂pin₂ (0.30 mmol), NaOt-Bu (20 mol %), Cu(CH₃CN)₂PF₆ (10 mol %), (R)-DM-Segphos (11 mol %), MeOH (0.8 mmol), THF (0.2 M). [b] Yield of isolated 2. [c] ee value as determined by chiral SFC or HPLC previous oxidation of the C–B bond. [d] ee value as determined by chiral SFC.
The Cu complexes formed after the alkene insertion show a long Cu–C distance with the C atom involved in the reaction \( \text{II}_{g} \) and \( \text{II}_{i} \); see Scheme 4. In fact, the structure is reminiscent of a (\( \pi \)-allyl)Cu complex. These complexes would become protonated in a subsequent step. We have also calculated the energy for isomer \( \text{II}_{g} \) corresponding to the slipping of the borylated substrate to afford a copper-phenoxide complex \( \text{II}_{s} \). This process is highly exoergic, and for that reason, we propose that protonation most likely takes place at the Cu–O bond. In summary, we have developed a new method for the asymmetric synthesis of useful monobenzylic and dibenzylic derivatives. Calculations at the density functional theory (DFT) level fully agree with experimental observations and provide insight for the development of new asymmetric transformations.

**REFERENCES**

(1) (a) Hall, D. In Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine; Hall, D., Ed.; Wiley-VCH: Weinheim, Germany, 2005. For recent applications of chiral secondary boronic esters, see: (b) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. J. Am. Chem. Soc. 2014, 136, 5828. (c) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. Nat. Chem. 2014, 6, 584. (d) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. Nature 2014, 513, 183. (e) Rasappan, R.; Aggarwal, V. K. Nat. Chem. 2014, 6, 810. (f) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. J. Am. Chem. Soc. 2012, 134, 16449. (g) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. J. Am. Chem. Soc. 2011, 133, 16794.

(2) For biologically active diaryl derivatives, see the following. For diarylmethanols: (a) Miki, T.; Kori, M.; Mabuchi, H.; Tozawa, R.; Nishimoto, T.; Sugiyama, Y.; Teshima, K.; Yokumasa, H. J. Med. Chem. 2002, 45, 4571. For diarylamines: (b) Spencer, C. M.; Faulds, D.; Peters, D. H. Drug Texts 1993, 46, 1055. For diarylmethanes: (c) Guay, D.; Hamel, P.; Blouin, M.; Brideau, C.; Chan, C. C.; Charette, N.; Ducharme, Y.; Huang, Z.; Girard, M.; Jones, T. R.; Laliberté, F.; Masson, P.; McAlulfe, M.; Pietucha, H.; Silva, J.; Young, R.; Girard, Y. Bioorg. Med. Chem. Lett. 2002, 12, 1457. For triarylmethanes: (d) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. Bioorg. Med. Chem. Lett. 2008, 18, 289.

(3) (a) Tortosa, M. Angew. Chem., Int. Ed. 2011, 50, 3950. (b) Alfaro, R.; Parra, A.; Aleman, J.; Garcia Ruano, J. L.; Tortosa, M. J. Am. Chem. Soc. 2014, 136, 12083.
For the only previous example of enantioselective 1,6-copper-catalyzed borylation of acyclic α,β,δ-unsaturated esters, see: Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. Angew. Chem., Int. Ed. Engl. 2015, 54, 1385.

(4) For seminal publications on 1,4-copper-catalyzed borylations, see: (a) Takahashi, K.; Ishiyama, T.; Miyaura, N. Chem. Lett. 2000, 982. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. J. Organomet. Chem. 2001, 625, 47. (c) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. Tetrahedron Lett. 2000, 41, 6821. For representative examples of enantioselective 1,4-copper-catalyzed borylations of electron-poor alkenes, see: (d) Hormillos, V.; Vila, C.; Otten, E.; Feringa, B. L. Angew. Chem., Int. Ed. 2015, 54, 7867. (e) Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T. Angew. Chem., Int. Ed. 2012, 51, 12763. (f) Hartmann, E.; Oestreich, M. Org. Lett. 2012, 14, 2406. (g) Burns, A. R.; Solana Gonzalez, J. S.; Lam, H. W. Angew. Chem., Int. Ed. 2012, 51, 10827. (h) Moure, A. L.; Gomez Arrayas, R.; Carretero, J. C. Chem. Commun. 2011, 47, 6701. (i) Lee, J. C.; McDonald, R.; Hall, D. G. Nat. Chem. 2011, 3, 894. (j) Fernandez, E.; Gulyas, H.; Sole, C.; Mata, J. A.; Tatla, A.; Whiting, A. Chem. - Eur. J. 2011, 17, 14248. (k) O’Brien, M. J.; Lee, K.-S.; Hoveyda, A. H. J. Am. Chem. Soc. 2010, 132, 10630. (l) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2009, 131, 11664. (m) Sim, H.-S.; Feng, X.; Yun, J. Chem.—Eur. J. 2009, 15, 1939. (n) Iizuka, S.; Nakagaki, N.; Kubo, M.; Itoh, T. J. Polym. Sci., Part A: Polym. Chem. 2010, 129, 5067. (o) Lillo, V.; Prieto, A.; Bonet, A.; Diaz-Requejo, M. M.; Ramirez, J.; Perez, P. J.; Fernandez, E. Organometalics 2009, 28, 659. (p) Lee, E.; Yun, J. Angew. Chem., Int. Ed. 2008, 47, 145.

(5) For recent reviews, see: (a) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Zheng, X.; Zeng, C.; Wu, Q.; Shi, F. Acc. Chem. Res. 2014, 47, 3655. (b) Pathak, T. P.; Sigman, M. S. J. Org. Chem. 2011, 76, 9210. (c) Caruana, L.; Fochi, M.; Bernardi, L. Molecules 2015, 20, 11733. For recent examples, see: (d) Hsiao, C.-C.; Raja, S.; Liao, H.-H.; Atodiresei, I.; Rueping, M. Angew. Chem., Int. Ed. 2015, 54, 5762. (e) Zhao, J.-J.; Sun, S.-B.; He, S.-H.; Wu, Q.; Shi, F. Angew. Chem., Int. Ed. 2015, 54, 5460. (f) Hsiao, C.-C.; Liao, H.-H.; Rueping, M. Angew. Chem., Int. Ed. 2014, 53, 13258. (g) Lu, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. Angew. Chem., Int. Ed. 2013, 52, 8607. (h) Izquierdo, J.; Orue, A.; Scheidt, K. A. J. Am. Chem. Soc. 2013, 135, 10634. (i) Luan, Y.; Schaus, S. E. J. Am. Chem. Soc. 2012, 134, 19965. (j) Jensen, K. H.; Webb, J. D.; Sigman, M. S. J. Am. Chem. Soc. 2010, 132, 17471–17482. (k) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. J. Am. Chem. Soc. 2009, 131, 17074. (l) Zhang, Y.; Sigman, M. S. J. Am. Chem. Soc. 2007, 129, 3076. (m) Mattson, A. E.; Scheidt, K. J. Am. Chem. Soc. 2007, 129, 4508. (n) Gilgorich, K. M.; Schultz, M. J.; Sigman, M. S. J. Am. Chem. Soc. 2006, 128, 2794. (o) Schultz, M. J.; Sigman, M. S. J. Am. Chem. Soc. 2006, 128, 1460.

(7) (a) Caruana, L.; Kniep, F.; Johansen, T. K.; Poulsen, P. H.; Jorgensen, K. A. J. Am. Chem. Soc. 2014, 136, 15929. (b) Chu, W.-D.; Zhang, H.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Wang, M.; Cui, J. Angew. Chem., Int. Ed. 2015, 54, 1385.

(8) For a recent highlight, see: Parra, A.; Tortosa, M. ChemCatChem 2015, 7, 1524.

(9) (a) Parra, A.; Jarava, C.; López, A.; Cruz, F.; Tortosa, M. Asymmetric synthesis of Versatil Benzonic Boronic Esters through a Borylation-Aromation Process. Presented at the 18th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 18), Sitges—Barcelona, Spain, June 28–July 2, 2015; Paper No. P-065. (b) López, A.; Jarava, C.; Parra, A.; Cruz, F.; Tortosa, M. Asymmetric Synthesis of Versatil Benzonic Boronic Esters through a Borylation-Aromation Process. Presented at the 19th European Symposium of Organic Chemistry (ESOC2015), Lisboa, Spain, July 12–16, 2015; Paper No. P181. (c) Jarava, C.; López, A.; Parra, A.; Cruz, F.; Tortosa, M. Asymmetric Synthesis of Versatil Benzonic Boronic Esters through a Borylation-Aromation Process. Presented at the XXXV Spanish Biannual Chemistry Congress, A Coruña, Spain, July 19–23, 2015; Paper No. S3-FC-12.

(10) During the preparation of this manuscript, Liao et al. published a closely related paper using a sulfoxide-phosphine ligand (published online Aug. 28, 2015): Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. Angew. Chem., Int. Ed. 2015, 54, 12134.1002/ anie.201505926 We have observed similar enantioselectivities using a commercially available ligand and running the reaction at room temperature. In addition, our catalytic system can overcome some of the structural limitations found in the excellent work by Liao.

(11) For a review on the use of the t-Bu group as a protecting group in the synthesis of aromatic compounds, see: Saleh, S. A.; Tashtoush, H. I. Tetrahedron 1998, 54, 14157.

(12) For a full account on all the ligands used and other parameters, see the Supporting Information.

(13) CCDC 1405406 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html. The absolute configuration of the other dibenzylboronates was assigned by analogy.

(14) 1H NMR experiments at shorter reaction times did not show olefin isomerization of the starting E/Z mixture.

(15) We have proposed a stereochemical model based on DFT calculations, which reflect steric interactions between the double bond substrate and the ligand play an important role in the stereodiscrimination. See Supporting Information for details.

(16) Formation of these adducts is endoergic, for entropy reasons, as expected for an associative process. Other higher-energy real coordination complexes could be located (see Supporting Information, Figure), but they are not productive, since they are not connected to the transition states, as shown by IRC studies.

(17) We cannot rule out direct reaction of the copper phenoxide with Bpin, to generate a borylated phenol and a copper(I)-boryl complex that would start over the catalytic cycle.