Synthesis of BCP-Based Straight-Shaped Diphosphine Ligands

Hideaki Takano,[a,b] Hitomi Katsuyama,[a,b] Hiroki Hayashi, [a,b] Miyu Harukawa,[c] Makoto Tsurui,[c] Sunao Shoji,[a,c] Yasuchika Hasegawa,[a,c] Satoshi Maeda, [a,b,d,e] and Tsuyoshi Mita*[a,b]

[a]   Dr. H. Takano, H. Katsuyama, Dr. H. Hayashi, Dr. S. Shoji, Prof. Y. Hasegawa, Prof. S. Maeda, Prof. T. Mita
        Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University
        Kita 21, Nishi 10, Kita-ku, Sapporo, Hokkaido 001-0021, Japan
        E-mail: tmita@icredd.hokudai.ac.jp
[b]   Dr. H. Takano, H. Katsuyama, Dr. H. Hayashi, Prof. S. Maeda, Prof. T. Mita
        JST, ERATO Maeda Artificial Intelligence in Chemical Reaction Design and Discovery Project
        Kita 10, Nishi 8, Kita-ku, Sapporo, Hokkaido 060-0810, Japan
[c]   M. Harukawa, M. Tsurui, Dr. S. Shoji, Prof. Y. Hasegawa
        Faculty of Engineering, Hokkaido University,
        Kita 13, Nishi 8, Kita‑Ku, Sapporo, Hokkaido 060‑8628, Japan
[d]   Prof. S. Maeda
        Department of Chemistry, Faculty of Science, Hokkaido University
        Kita 10, Nishi 8, Kita-ku, Sapporo, Hokkaido 060-0810, Japan
[e]   Prof. S. Maeda
        Research and Services Division of Materials Data and Integrated System (MaDIS), National Institute for Materials Science (NIMS)
   Tsukuba, Ibaraki 305-0044, Japan

        Supporting information for this article is given via a link at the end of the document.

Abstract: [1.1.1]Propellane, which is structurally simple and compact, exhibits promising potential for the synthesis of disubstituted straight-shaped bicyclo[1.1.1]pentane (BCP) compounds by manipulation of its highly reactive internal C–C bond. BCPs are considered to be isosteres of 1,4-disubstituted benzenes, which have found broad applications in the areas of functional molecules and drug discovery. The internal C–C single bond of [1.1.1]propellane is regarded as a change-shift bond, which can be readily cleaved by radical or ionic means to construct BCPs. We herein report a novel synthetic method for (un)symmetric diphosphines based on the BCP motif, which can be interpreted as isosteres of 1,4-bis(diphenylphosphino)benzenes. The obtained BCP-diphosphine derivatives were used to generate a straight-shaped Au complex and a Eu-based coordination polymer.

Diphosphines, which are frequently used as ligands due to their facile coordination to transition-metal salts, are extremely useful in organic synthesis. Among the various hitherto reported diphosphines, the structural motif of the diphosphino*ethane* (R_2P–CH_2–CH_2–PR_2) has attracted significant attention as a bidentate chelating ligand to create stable five-membered metallacycles with transition metals, which promote a variety of catalytic transformations (Figure 1a).[1] On the other hand, straight-shaped diphosphine ligands have also been extensively studied, because these molecules have shown unique structural and physical properties in supramolecular chemistry. In this context, numerous 1,4-disubstituted benzene-diphosphine derivatives (R_2P–*p*-C_6H_4–PR_2) have been employed for the coordination to various transition metals such as Cu and Au to generate multinuclear cyclic or polymeric structures (Figure 1b).[2] These distinct characteristics encouraged us to synthesize analogous straight-shaped skeletons, which will facilitate the further exploration of this field.

[1.1.1]Propellane has attracted significant interest due to recent novel transformations wherein a variety of nucleophiles or radical species add to the highly strained internal C–C bond to generate bicyclo[1.1.1]pentanes (BCPs).[3] Some BCPs exhibit notable biological activity such as increased permeability, aqueous solubility, and metabolic stability owing to their bioisosteric character as 1,4-disubstituted benzene, *tert*-butyl, or alkyne.[3,4] Considering the ready availability of [1.1.1]propellane, we have become greatly interested in the synthesis of BCP-based

diphosphines from [1.1.1]propellane as the starting material. Changing the two-dimensional (essentially planar) structure of benzene to the three-dimensional non-planar structure of BCP can be expected to produce diphosphines with very interesting structural and physical properties (Figure 1c). To the best of our knowledge, this type of diphosphine ligand is very rare, and only a few examples of symmetric BCP-diphosphine dioxide derivatives have been reported so far.[5] Our recent radical difunctionalization of ethylene with phosphine oxide and chlorophosphine to synthesize (un)symmetric 1,2-bis(diphenylphosphino)ethane derivatives[6] inspired us to synthesize BCP-diphosphine compounds from [1.1.1]propellane via this radical difunctionalization because the internal C–C bond of [1.1.1]propellane can be cleaved homolytically under radical conditions.[4]
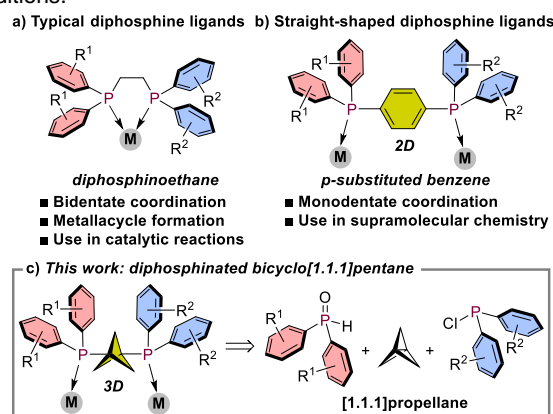

Figure 1. Our design for bidentate phosphine ligands based on [1.1.1]propellane.

We herein report the synthesis of (un)symmetric BCP-diphosphines under photochemical conditions using blue and white light. In terms of the synthetic utility of these BCP-diphosphine compounds, we demonstrate the facile complexation with (THT)AuC$_6$F$_5$ (THT: tetrahydrothiophene). The straight-shaped structure of the resulting complex was confirmed by single-crystal X-ray diffraction analysis. Furthermore, an

unsymmetric Eu-based coordination polymer was successfully prepared from an unsymmetric BCP-diphosphine dioxide.

Table 1. Optimization of the Reaction Conditions
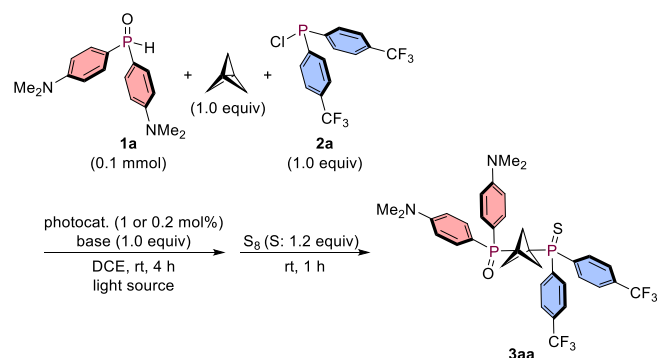
| Entry	Photocatalyst	Base	Light	Yield[a] (%)
1	Ir(ppy)₃	DBU	Blue	58
2	[Ir(ppy)₂(dtbbpy)]PF₆	DBU	Blue	58
3	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	DBU	Blue	61
4	[Ru(bpy)₃](PF₆)₂	DBU	Blue	29
5	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	TMG	Blue	61
6[b]	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	2,6-lutidine	Blue	50
7[c]	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	Cs₂CO₃	Blue	11
8	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	Hünig's base	Blue	52
9	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	TEA	Blue	68
10[b]	—	TEA	White	74
11	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	TEA	—	13
12	—	TEA	—	20
13[c]	[Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆	TEA	Blue	(75)
14[b,c]	—	TEA	White	(74)

Conditions: photocatalyst (1 mol%), **1a** (0.1 mmol), [1.1.1]propellane (1.0 equiv, 0.3–0.5 M in diethyl ether), **2a** (1.0 equiv), DBU (1.0 equiv), DCE (0.3 mL), rt, 4 h, and two LEDs. [a]Yields were determined via ¹H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard. [b]The reaction time was 24 h. [c]Photocatalyst (0.2 mol%), **1a** (0.5 mmol), [1.1.1]propellane (0.5 mmol in 0.3-0.5 M in diethyl ether), **2a** (1.0 equiv), DBU (1.0 equiv), DCE (1.5 mL), and two LEDs.

Based on our previous radical difunctionalization of ethylene,[6] we first screened potential reaction conditions for the three-component reaction (3CR) of a phosphine oxide ((p-NMe₂-C₆H₄)₂P(=O)H (**1a**): 0.1 mmol), [1.1.1]propellane (1 equiv), and a chlorophosphine ((p-CF₃-C₆H₄)₂PCl (**2a**): 1 equiv) in the presence of 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under irradiation with light (Table 1). We first examined various photocatalysts (1 mol%) under irradiation from blue LEDs. Among the various Ir catalysts investigated, Ir(ppy)₃, [Ir(ppy)₂(dtbbpy)]PF₆, and [Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆ exhibited similar levels of conversion (entries 1–3), whereby [Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆ gave a slightly higher yield (entry 3). The use of the Ru-based photocatalyst [Ru(bpy)₃](PF₆)₂ produced the desired product **3aa** in only 29% yield (entry 4). Among the photocatalysts examined, we chose [Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆ as the optimal catalyst for the further screening of the reaction conditions (entry 3). We next investigated the use of a variety of bases, namely, 1,1,2,2-tetramethylguanidine (TMG), 2,6-lutidine, Cs₂CO₃, diisopropylethylamine (Hünig's base), and triethylamine (TEA) (entries 5–9). Although **3aa** was obtained in 61% using TMG (entry 5), the use of 2,6-lutidine, Cs₂CO₃ and Hünig's base decreased the yield (entries 6–8). However, when TEA was used, the yield increased to 68% (entry 9). White LED light, which is a user-friendly light source that covers all wavelengths of the

visible-light region, also promoted the 3CR in 74% yield, even in the absence of a photocatalyst. A thermal reaction under the complete exclusion of light also promoted the 3CR, whereby **3aa** was formed in 13% and 20% yield with and without the photocatalyst (entries 11 and 12), respectively, which indicates that the 3CR is significantly accelerated by photoirradiation. Finally, preparative-scale (0.5 mmol) reactions conducted under irradiation from blue LEDs with the photocatalyst or from white LEDs without a photocatalyst promoted the 3CR efficiently, and **3aa** was obtained in 75% and 74% yield, respectively after isolation (entries 13 and 14).

We then investigated the substrate scope for the synthesis of unsymmetric BCP derivatives using different phosphine oxides (Ar¹₂P(O)H) and chlorophosphines (Ar²₂PCl; Ar¹ ≠ Ar²) under two different sets of reaction conditions: A) in the presence of an Ir photocatalyst under irradiation from blue LEDs (λ_{ex} = 440 nm) for 4 h, and B) in the absence of a photocatalyst under irradiation from white LEDs for 24 h (Figure 2). Electron-donating p-NMe₂-C₆H₄)₂P(=O)H (**1a**) was first chosen as the phosphine unit to screen the chlorophosphine part. Not only **1a**, but also diphenyl-substituted chlorophosphine **2b**, underwent the 3CR to afford product **3ab** in good yield (57% and 58%) under the two sets of reaction conditions. The electron-withdrawing chlorophosphines **2c-e**, which bear p-fluoro (**2c**), p-chloro (**2d**), and 3,5-diCF₃ (**2e**) groups on the phenyl rings, also efficiently promoted the 3CR to furnish **3ac**, **3ad**, and **3ae**, respectively. Next, the electron-withdrawing (p-CF₃-C₆H₄)₂PCl (**2a**) was fixed as the chlorophosphine unit for further screening of various phosphine oxides. Substituents with electron-donating (4-MeO, p-t-Bu, and DTBM) groups on the phenyl rings were suitable for the 3CR to afford the desired products (**3ba**, **3ca**, and **3da**) in moderate-to-high yield under either set of reaction conditions. 1-Naphthelene-substituted **3ea** was also obtained in good yield. A symmetric BCP (**3fb**) with electronically neutral phenyl substituents could also be synthesized under irradiation from both blue and white LEDs in 80% and 74% yield, respectively. The larger-scale synthesis of **3fb** was achieved with similar efficiency using 5 mmol of **1f** and **2b**. We also investigated the 3CR of dialkylphosphine oxide (cyclohexyl and $tert$-butyl), chlorodiphenylphosphine (**2b**), and [1.1.1]propellane, however, their reaction systems were messy and the target compounds were not obtained.

We then investigated the conversion of unsymmetric **3aa** and symmetric **3fb** to diphosphine dioxide **4aa** and **4fa** as well as diphosphine ligands **5aa** and **5fb**, which further demonstrated the utility of unsymmetric **4aa** and **5aa** (Figure 3). After oxidative exchange of S to O on the phosphine sulfide moiety by treatment with mCPBA, the corresponding dioxides **4aa** and **4fb** were obtained in high yield. Dioxides **4aa** and **4fb** were readily reduced using air-stable 1,3-diphenyl-disiloxane (PhH₂Si–O–SiH₂Ph; DPDS)[7] in toluene to afford unsymmetric **5aa** and symmetric **5fb** in good yield under conditions that do not require glove-box techniques. The obtained unsymmetric diphosphine **5aa** was treated with (THT)AuC₆F₅ (THT: tetrahydrothiophene), and the subsequent complex formation proceeded readily to afford the corresponding diphosphine-Au complex **6aa** in high yield. Its three-dimensional structure was unambiguously determined using single-crystal X-ray diffraction analysis[8] (for details, see the Supporting Information) to reveal that each phosphine atom coordinates to a different Au atom to create a straight-shaped molecule.
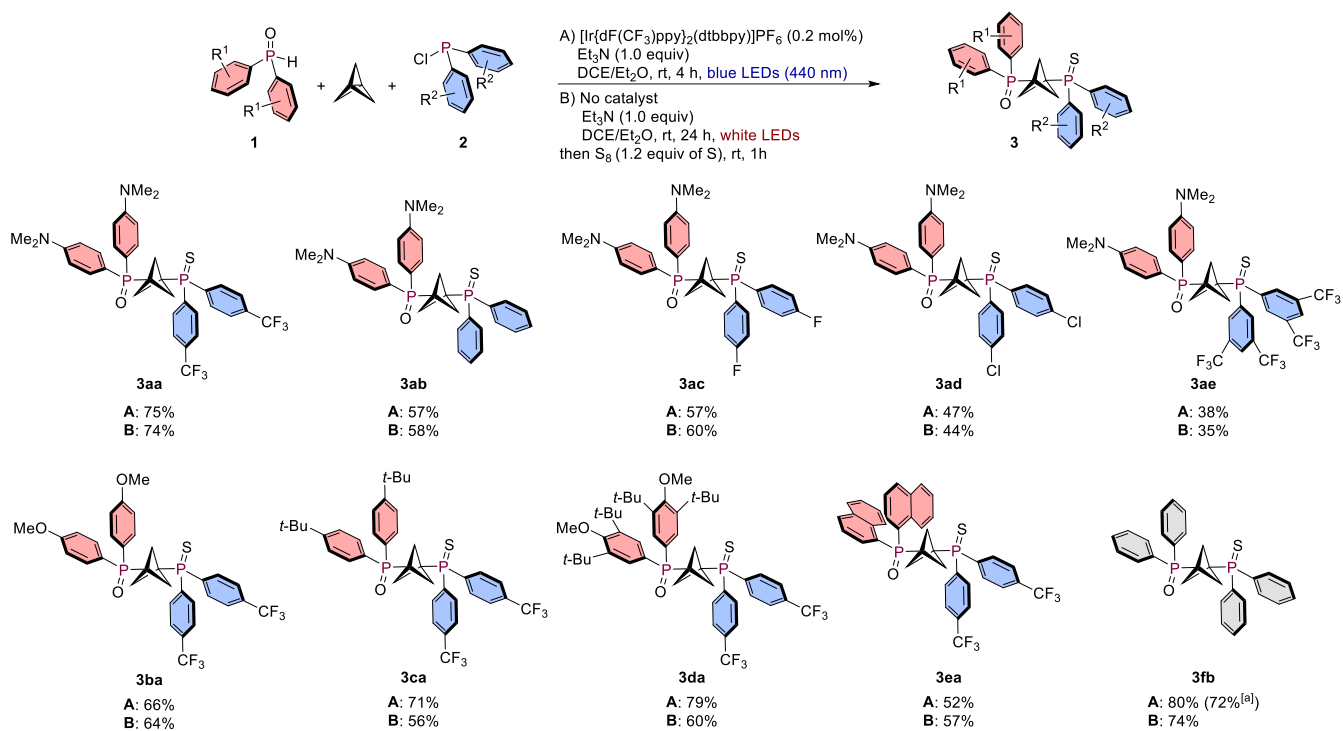
Figure 2. Scope of symmetric and unsymmetric BCP derivatives obtained in this study. Conditions A: Ir catalyst (0.001 mmol), **1** (0.5 mmol), [1.1.1]propellane (0.5 mmol), **2** (0.5 mmol), DBU (0.5 mmol), DCE (1.5 mL), rt, 4 h, and two blue LEDs. Conditions B: **1** (0.5 mmol), [1.1.1]propellane (0.5 mmol), **2** (0.5 mmol), DBU (0.5 mmol), DCE (1.5 mL), rt, 24 h, and two white LEDs. [a] Scale: 5 mmol.
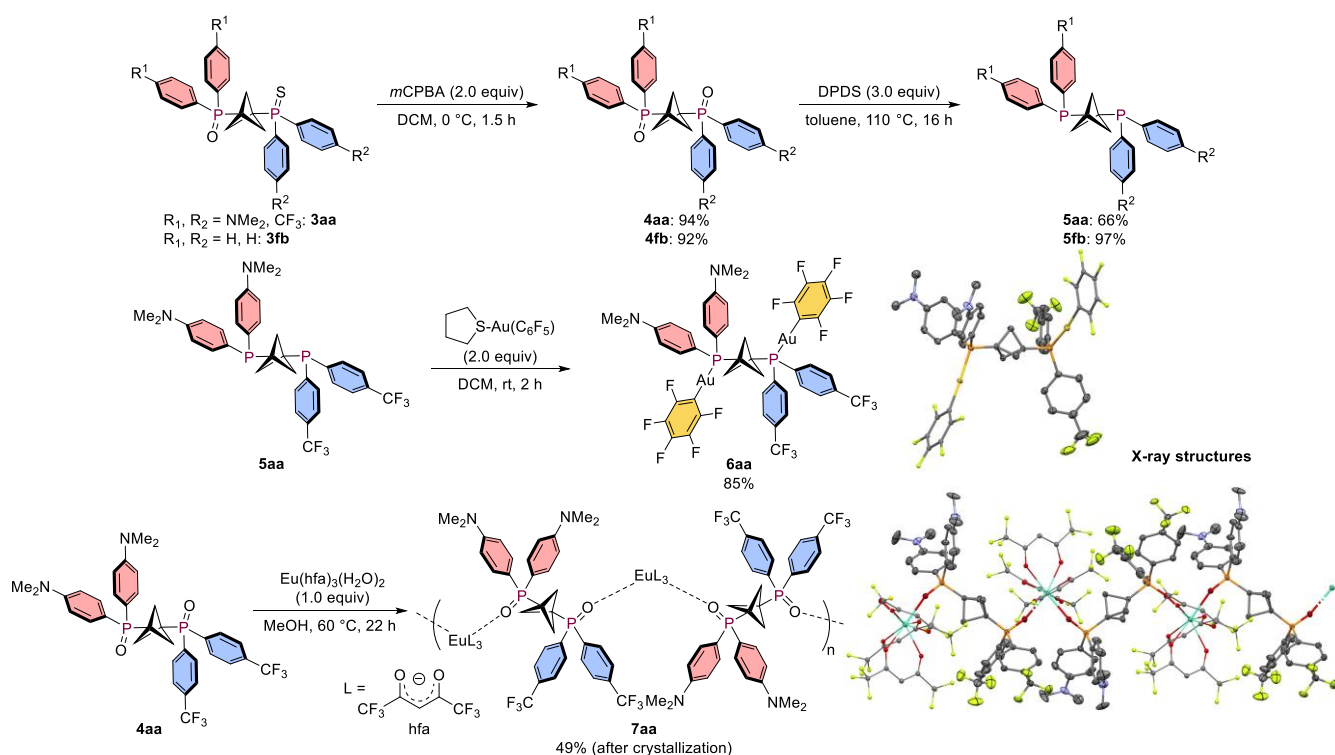
Figure 3. Synthesis of the Au complex **6aa** and Eu-based coordination polymer **7aa**. Thermal ellipsoids are shown at the 30% probability level; all hydrogen atoms are omitted for clarity.

Furthermore, unsymmetric dioxide **4aa** was treated with Eu(hfa)$_3$(H$_2$O)$_2$ (hfa = hexafluoroacetylacetonate) to give the corresponding Eu-based coordination polymer **7aa** in 34% yield after crystallization. A single-crystal X-ray diffraction analysis[8]

3

clearly indicated that each europium ion is coordinated by three hfa ligands and two phosphine oxide moieties, each of which has different electronic character, i.e., an electron-donating and an electron-withdrawing phosphine oxide, to form an octacoordinated metal center. This unique coordination mode creates a well-aligned polymeric structure that might be useful for luminescent photonic materials. We are currently investigating the optical properties of this polymeric complex.

Finally, we theoretically examined the mechanism of the light-promoted radical reaction with the support of DFT calculations using symmetric $Ph_2P(=O)-PPh_2$ (**7fb**), which should be initially generated from **1f** and **2b** in the presence of a base.[6] The calculations were carried out using the AFIR method[9] at the $U\omega B97X-D/Def2-SVP$ level in dichloromethane (SMD model). Under irradiation from blue LEDs, $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ absorbs light at 440 nm and is excited to its triplet state (ΔE_T = 61.8 kcal/mol),[10] which then transfers energy to **7fb** to excite it to the triplet state (ΔG = 44.7 kcal/mol). Using white LEDs, **7fb** directly absorbs light to promote its radical dissociation (Figure 4).[6,11] Simultaneous dissociation of the P(=O)−P single bond occurs from its triplet state, and the resulting phosphoryl radical ($Ph_2P(=O)\cdot$) reacts with [1.1.1]propellane to generate the tertiary alkyl radical ($\Delta G^{\ddagger}$ = 8.5 kcal/mol). Compared to the radical addition of the phosphinyl radical ($Ph_2P\cdot$) ($\Delta G^{\ddagger}$ = 10.7 kcal/mol), the electron-withdrawing phosphonyl radical is more reactive toward [1.1.1]propellane. The resulting tertiary-alkyl radical may react associatively with the remaining phosphinyl radical (radical–radical coupling). However, both the tertiary-alkyl radical and the phosphinyl radical exhibit transient character,[12] and their concentration seems to be very low. Hence, we calculated another possibility involving a radical-chain mechanism, which revealed an energy barrier of 7.8 kcal/mol for the radical addition of the tertiary-alkyl radical to diphosphine **7fb**. Based on the activation barrier for radical-chain addition, which can be reasonably overcome at room temperature, we think that the radical-chain process governs the reaction. We also calculated

the reactivity of the tertiary-alkyl radical to another molecule of [1.1.1]propellane, whose dimerization has been considered computationally in the literature.[4e,h] Our calculations also proved that the activation energy for the radical dimerization of [1.1.1]propellane is higher than that of the expected radical-chain pathway, which supports our experimental results that no dimerization products were observed.

In summary, we have developed a method for the diphosphination of [1.1.1]propellane under irradiation from blue LEDs in the presence of an Ir-based photocatalyst or under irradiation from white LEDs in the absence of a catalyst, which efficiently promoted the radical diphosphination of [1.1.1]propellane using a phosphine oxide and a chlorophosphine. A reasonable reaction mechanism involving radical propagation was elucidated using DFT calculations. A BCP-based diphosphine and a BCP-based diphosphine dioxide were transformed into a straight-shaped Au complex and a well-aligned Eu-based coordination polymer, respectively. We are currently intensively studying applications of such BCP-based diphosphines. We are convinced that this study will contribute not only to materials science, but also to a better understanding of the reactivity of strained [1.1.1]propellane derivatives.

Acknowledgements
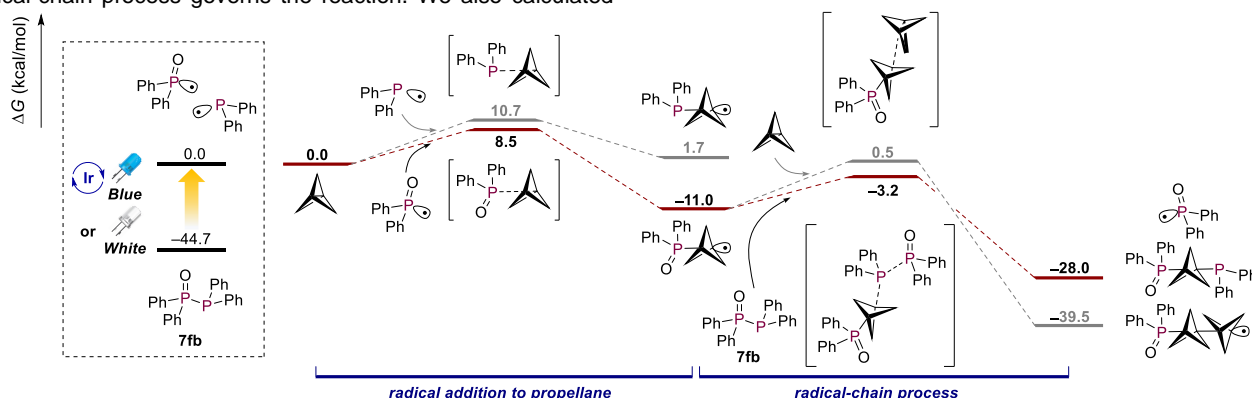
Figure 4. Plausible reaction mechanism based on DFT calculations. The reaction diagrams were calculated at the $U\omega B97X-D/Def2-SVP/SMD(DCM)$ level.

[1] P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741-2770.

[2] a) G. Jia, R. J. Puddephatt, J. D. Scott, J. J. Vittal, *Organometallics* **1993**, *12*, 3565-3574; b) D. Imhof, U. Burckhardt, K.-H. Dahmen, F. Joho, R. Nesper, *Inorg. Chem.* **1997**, *36*, 1813-1820; c) P. M. Van Calcar, M. M. Olmstead, A. L. Balch, *Inorg. Chim. Acta.* **1998**, *270*, 28-33; d) D. Li, Q. Feng, X.-L. Feng, J.-W. Cai, *Inorg. Chem. Commun.* **2003**, *6*, 361-364;

e) I. O. Koshevoy, A. J. Karttunen, S. P. Tunik, M. Haukka, S. I. Selivanov, A. S. Melnikov, P. Y. Serdobintsev, M. A. Khodorkovskiy, T. A. Pakkanen, *Inorg. Chem.* **2008**, *47*, 9478-9488; f) I. O. Koshevoy, A. J. Karttunen, Y.-C. Lin, C.-C. Lin, P.-T. Chou, S. P. Tunik, M. Haukka, T. A. Pakkanen, *Dalton Trans.* **2010**, *39*, 2395-2403; g) J. Rohacova, A. Sekine, T. Kawano, S. Tamari, O. Ishitani, *Inorg. Chem.* **2015**, *54*, 8769-8777; h) V. Fernández-Moreira, J. Cámara, E. S. Smirnova, I. O. Koshevoy, A. Laguna, S. P. Tunik, M. C. Blanco, M. C. Gimeno, *Organometallics* **2016**, *35*, 1141-1150.

[3]   For reviews on BCP compounds, see: a) K. B. Wiberg, *Angew. Chem., Int. Ed.* **1986**, *25*, 312-322; *Angew. Chem.* **1986**, *98*, 312-322; b) J. Kanazawa, M. Uchiyama, *Synlett* **2019**, *30*, 1-11; c) J. Turkowska, J. Durka, D. Gryko, *Chem. Commun.* **2020**, *56*, 5718-5734.

[4]   K. B. Wiberg, S. T. Waddell, *J. Am. Chem. Soc.* **1990**, *112*, 2194-2216; b) C. B. Kelly, A. M. Colthart, B. D. Constant, S. R. Corning, L. N. E. Dubois, J. T. Genovese, J. L. Radziewicz, E. M. Sletten, K. R. Whitaker, L. J. Tilley, *Org. Lett.* **2011**, *13*, 1646-1649; c) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241-246; d) R. A. Shelp, P. J. Walsh, *Angew. Chem., Int. Ed.* **2018**, *57*, 15857-15861; *Angew. Chem.* **2018**, *130*, 16083-16087; e) J. H. Kim, A. Ruffoni, Y. S. S. Al-Faiyz, N. S. Sheikh, D. Leonori, *Angew. Chem., Int. Ed.* **2020**, *59*, 8225-8231; *Angew. Chem.* **2020**, *132*, 8302-8308; f) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan, *Nature* **2020**, *580*, 220-226; g) W. Huang, S. Keess, G. A. Molander, *J. Am. Chem. Soc.* **2022**, *144*, 12961-12969; h) Y. Kraemer, C. Ghiazza, A. N. Ragan, S. Ni, S. Lutz, E. K. Neumann, J. C. Fettinger, N. Nöthling, R. Goddard, J. Cornella, C. R. Pitts, *Angew. Chem., Int. Ed.* **2022**, e202211892; *Angew. Chem.* **2022**, *134*, e202211892; i) N. Frank, J. Nugent, B. R. Shire, H. D. Pickford, P. Rabe, A. J. Sterling, T. Zarganes-Tzitzikas, T. Grimes, A. L. Thompson, R. C. Smith, C. J. Schofield, P. E. Brennan, F. Duarte, E. A. Anderson, *Nature* **2022**, *611*, 721-726; j) T. Iida, J. Kanazawa, T. Matsunaga, K. Miyamoto, K. Hirano, M. Uchiyama, *J. Am. Chem. Soc.* **2022**, *144*, 21848-21852.

[5]   a) P. Kaszynski, A. C. Friedli, J. Michl, *J. Am. Chem. Soc.* **1992**, *114*, 601-620; b) Z. Spichal, A. Jancarik, C. Mazal, J. Pinkas, P. Pekarkova, M. Necas, *Polyhedron* **2013**, *62*, 83-88.

[6]   H. Takano, H. Katsuyama, H. Hayashi, W. Kanna, Y. Harabuchi, S. Maeda, T. Mita, *Nat. Commun.* **2022**, *13*, 7034.

[7]   J. A. Buonomo, C. G. Eiden, C. C. Aldrich, *Chem. Eur. J.* **2017**, *23*, 14434-14438.

[8]   CCDC 2223219 (**6aa**) and 2234630 (**7aa**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre. For details, see the Supporting Information.

[9]   For the AFIR method implemented in the GRRM program, see: a) S. Maeda, K. Ohno, K. Morokuma, *Phys. Chem. Chem. Phys.* **2013**, *15*, 3683-3701; b) S. Maeda, T. Taketsugu, K. Morokuma, *J. Comput. Chem.* **2014**, *35*, 166-173; c) S. Maeda, Y. Harabuchi, M. Takagi, K. Saita, K. Suzuki, T. Ichino, Y. Sumiya, K. Sugiyama, Y. Ono, *J. Comput. Chem.* **2018**, *39*, 233-251; d) S. Maeda, Y. Harabuchi, *WIREs Comput. Mol. Sci.* **2021**, *11*, e1538.

[10]   F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer, F. Glorius, *Chem. Soc. Rev.* **2018**, *47*, 7190-7202.

[11]   M. Nakajima, S. Nagasawa, K. Matsumoto, T. Kuribara, A. Muranaka, M. Uchiyama, T. Nemoto, *Angew. Chem., Int. Ed.* **2020**, *59*, 6847-6852; *Angew. Chem.* **2020**, *132*, 6914-6919.

[12]   S. K. Wong, W. Sytnyk, J. K. S. Wan, *Can. J. Chem.* **1971**, *49*, 994-1000.