Inorg. Chem. **2005**, *44*, 410–415

Inorganic Chemistry
Article

# Carbon–Halogen Bond Activation Mechanism by Copper(I) Complexes of (2-Pyridyl)alkylamine Ligands

**Takao Osako,**[†] **Kenneth D. Karlin,***[,‡] **and Shinobu Itoh***[,†]

*Department of Chemistry, Graduate School of Science, Osaka City University, 3-3-138 Sugimoto,*
*Sumiyoshi-ku, Osaka 558-8585, Japan, and Department of Chemistry, Johns Hopkins University,*
*Baltimore, Maryland 21218*

Received August 10, 2004

The reaction of *p*-substituted benzyl halides ($^{Y}$BnX; X = Cl, Br, and I; Y = *p*-substituent, OMe, *t*-Bu, Me, H, F, Cl, and $NO_2$) and copper(I) complexes supported by a series of (2-pyridyl)alkylamine ligands has been investigated to shed light on the mechanism of copper(I) complex mediated carbon–halogen bond activation, including ligand effects on the redox reactivity of copper(I) complexes which are relevant to the chemistry. For both the tridentate ligand $^{Phe}L^{Pym2}$ [*N*,*N*-bis(2-pyridylmethyl)-2-phenylethylamine] and tetradentate ligand TMPA [tris(2-pyridylmethyl)-amine] complexes, the C–C coupling reaction of benzyl halides proceeded smoothly to give corresponding 1,2-diphenylethane derivatives and copper(II)–halide complex products. Kinetic analysis revealed that the reaction obeys second-order kinetics both on the copper complex and the substrate; rate = $k[\mathrm{Cu}]^2[^{Y}\mathrm{BnX}]^2$. A reaction mechanism involving a dinuclear copper(III)–halide organometallic intermediate is proposed, on the basis of the kinetic results, including observed electronic effects of *p*-substituents (Hammett plot) and the rate dependence on the BDE (bond dissociation energy) of the C–X bond, as well as the ligand effects.

## Introduction

A large number of biomimetic transition-metal complexes supported by a wide variety of ligands have so far been developed to evaluate the active site structures and functions of many metalloenzymes.[1] For copper, a great deal of effort has been made especially in oxygen activation chemistry to provide profound insights into the catalytic mechanism of copper monooxygenases and copper oxidases.[2−4] Among the series of nitrogen donor ligands, (2-pyridyl)alkylamine ligands have played very important roles in exploring the structures and reactivities of copper−dioxygen intermediates.[2−6] Included are a series of tetradentate, tridentate, and didentate ligands developed by connecting (2-pyridyl)methyl ($PyCH_2$−; Pym) and 2-(pyridyl)ethyl ($PyCH_2CH_2$−; Pye) groups to the nitrogen atom(s) of ammonia ($NH_3$) and alkylamines ($RNH_2$ and RR′NH). One of the most familiar *tetradentate* ligands is TMPA (also called TPA, Chart 1), which was adopted for the synthesis of (*trans*-$\mu$-1,2-peroxo)-dicopper(II) complex **A**, the first structurally characterized copper−dioxygen complex (Chart 2).[7] It has been demonstrated that modifications of TMPA ligand by replacing one or two Pym moieties to Pye groups causes large effects on copper(I)−dioxygen reactivity.[8] For example, the copper(I) complex of TEPA (Chart 1), consisting of three Pye groups, exhibits virtually no reactivity toward molecular oxygen.[9]

Bis[2-(2-pyridyl)ethyl]amine tridentate ligands ($^{R}L^{Pye2}$, Chart 1) have also been widely employed in copper(I)/dioxygen chemistry. In contrast to the case of TMPA tetradentate ligand, the *tridentate* $^{R}L^{Pye2}$ ligands with −($CH_2$-$CH_2$)− linker (Pye) predominantly afford a side-on peroxodicopper(II) complex (**B**, Chart 2) in the reaction of the

---

* Authors to whom correspondence should be addressed. E-mail: shinobu@sci.osaka-cu.ac.jp (S.I.); karlin@jhu.edu (K.D.K.). Tel and fax: +81-6-6605-2564 (S.I.).

[†] Osaka City University.

[‡] Johns Hopkins University.

(1) Gavrilova, A. L.; Bosnich, B. *Chem. Rev.* **2004**, *104*, 349−383.
(2) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013−1045.
(3) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047−1076.
(4) Kim, E.; Chufán, E. E.; Kamaraj, K.; Karlin, K. D. *Chem. Rev.* **2004**, *104*, 1077−1133.
(5) Itoh, S.; Fukuzumi, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2081−2095.
(6) Schindler, S. *Eur. J. Inorg. Chem.* **2000**, 2311−2326.
(7) Tyeklár, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677−2689.
(8) Schatz, M.; Becker, M.; Thaler, F.; Hampel, F.; Schindler, S.; Jacobson, R. R.; Tyeklár, Z.; Murthy, N. N.; Ghosh, P.; Chen, Q.; Zubieta, J.; Karlin, K. D. *Inorg. Chem.* **2001**, *40*, 2312−2322.
(9) Karlin, K. D.; Hayes, J. C.; Juen, S.; Hutchinson, J. P.; Zubieta, J. *Inorg. Chem.* **1982**, *21*, 4106−4108.

10.1021/ic048902e CCC: $30.25

**Chart 1**

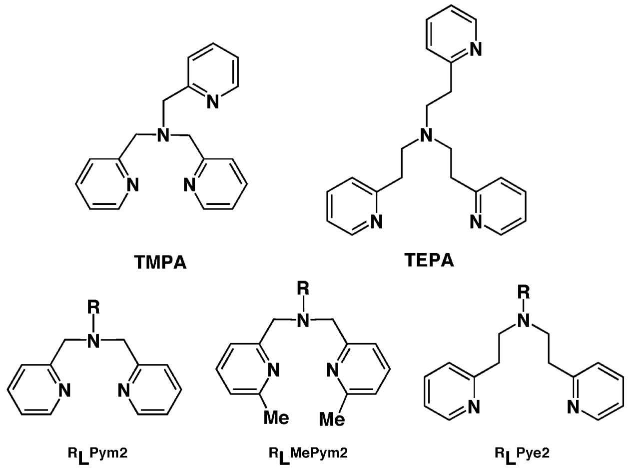
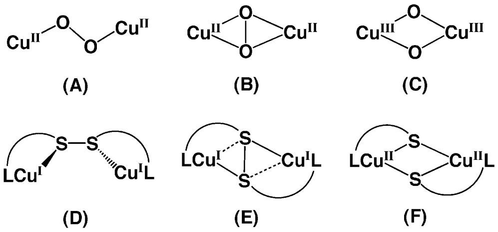


**Chart 2**



corresponding copper(I) complexes and dioxygen at a low temperature.[5,10−16] Furthermore, we have recently demonstrated that oxygenation of a copper(I) complex supported by the [bis(2-pyridyl)methyl]amine tridentate ligand ($^{R}L^{Pym2}$) with shorter methylene linker (Pym) provided a bis($\mu$-oxo)-dicopper(III) complex (**C**) instead of the peroxo complex **B**.[17] Moreover, it has been reported that the reactivity of copper(I) complexes is greatly affected by placement of a methyl group into the 6-position of a pyridine nucleus within chelating ligands.[18−20]

The different reactivity of copper(I) complexes toward $O_2$ can mostly be attributed to the difference in electron-donor ability of pyridine as well as ligand denticity (tetradentate vs tridentate). The electron-donor ability of pyridine is altered not only by changing the alkyl linker chain length ($-CH_2-$ in Pym vs $-CH_2CH_2-$ in Pye) but also by introducing a methyl group at the 6-position as $^{R}L^{MePym2}$ (Chart 1). Electron donor effects imparted by synthetically derived 4-pyridyl substituents also leads to measurable systematic variation in copper(I)−dioxygen chemistry with tridentate and tetradentate ligands.[15,16,21,22] Similar ligand effects have been found in the dicopper−disulfur complexes supported by a series of disulfide ligands $LCH_2CH_2S-SCH_2CH_2L$, where the redox state of copper as well as the $Cu_2S_2$ core structure is largely affected by the structure of metal binding site L ($^{R}L^{Pym2}$, $^{R}L^{MePym2}$, and $^{R}L^{Pye2}$), providing dicopper(I)−disulfide complexes with different core structures, **D** and **E**, and the bis($\mu$-thiolato)dicopper(II) complex **F**, as shown in Chart 2.[23,24]

As part of our continuing efforts to clarify the effects of ligands on the reactivity of copper(I) complexes, we herein investigated the C−C coupling reaction of benzyl halides by copper(I) complexes supported by the series of tridentate and tetradentate (2-pyridyl)alkylamine ligands shown in Chart 1 (eq 1).

$$2LCu^{I} + 2\,{}^{Y}BnX \rightarrow 2LCu^{II}X + {}^{Y}Bn-{}^{Y}Bn \qquad (1)$$

The C−C coupling reaction of alkyl halides by alkali and alkaline earth metals as well as several low-valent transition-metal ions are well-known in synthetic organic chemistry.[25] Lithium organocuprates are popular copper reagents for such a C−C coupling reaction.[26] However, the reaction of alkyl halides with simple copper(I) complexes such as those with (2-pyridyl)alkylamine ligands is relatively rare. In this regard, Karlin and co-workers reported that the copper(I) complex of TMPA (Chart 1) reacted efficiently with benzyl halide derivatives to give the corresponding C−C coupling dimer products and the corresponding copper(II)−halide complex as indicated in eq 1.[27] Formation of such copper(II)−halide complexes has also been reported recently in the reactions of related copper(I) complexes in the presence of organohalides such as $CH_2Cl_2$ or $CHCl_3$.[7,17,28−30] However, mechanistic details of such C−C coupling reactions have yet to be elucidated. The purpose of this study is to obtain further

---

(10) Karlin, K. D.; Kaderli, S.; Zuberbühler, A. D. *Acc. Chem. Res.* **1997**, *30*, 139−147.

(11) Pidcock, E.; Obias, H. V.; Abe, M.; Liang, H.-C.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1999**, *121*, 1299−1308.

(12) Pidcock, E.; Obias, H. V.; Zhang, C. X.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1998**, *120*, 7841−7847.

(13) Itoh, S.; Nakao, H.; Berreau, L. M.; Kondo, T.; Komatsu, M.; Fukuzumi, S. *J. Am. Chem. Soc.* **1998**, *120*, 2890−2899.

(14) Liang, H.-C.; Karlin, K. D.; Dyson, R.; Kaderli, S.; Jung, B.; Zuberbühler, A. D. *Inorg. Chem.* **2000**, *39*, 5884−5894.

(15) Henson, M. J.; Vance, M. A.; Zhang, C. X.; Liang, H.-C.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **2003**, *125*, 5186−5192.

(16) Zhang, C. X.; Liang, H.-C.; Kim, E.-i.; Shearer, J.; Helton, M. E.; Kim, E.; Kaderli, S.; Incarvito, C. D.; Zuberbuhler, A. D.; Rheingold, A. L.; Karlin, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 634−635.

(17) Osako, T.; Ueno, Y.; Tachi, Y.; Itoh, S. *Inorg. Chem.* **2003**, *42*, 8087−8097.

(18) Osako, T.; Tachi, Y.; Taki, M.; Fukuzumi, S.; Itoh, S. *Inorg. Chem.* **2001**, *40*, 6604−6609.

(19) Osako, T.; Suzuki, M.; Itoh, S. Unpublished results.

(20) Hayashi, H.; Fujinami, S.; Nagatomo, S.; Ogo, S.; Suzuki, M.; Uehara, A.; Watanabe, Y.; Kitagawa, T. *J. Am. Chem. Soc.* **2000**, *122*, 2124−2125.

(21) Shearer, J.; Zhang, C. X.; Hatcher, L. Q.; Karlin, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 12670−12671.

(22) Zhang, C. X.; Kaderli, S.; Costas, M.; Kim, E.-i.; Neuhold, Y. M.; Karlin, K. D.; Zuberbühler, A. D. *Inorg. Chem.* **2003**, *42*, 1807−1824.

(23) Itoh, S.; Nagagawa, M.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 4087−4088.

(24) Ueno, Y.; Tachi, Y.; Itoh, S. *J. Am. Chem. Soc.* **2002**, *124*, 12428−12429.

(25) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley: New York, 2000; p 537.

(26) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, 1987; p 682.

(27) Jacobson, R. R.; Tyeklár, Z.; Karlin, K. D. *Inorg. Chim. Acta* **1991**, *181*, 111−118.

(28) Komiyama, K.; Furutachi, H.; Nagatomo, S.; Hashimoto, A.; Hayashi, H.; Fujinami, S.; Suzuki, M.; Kitagawa, T. *Bull. Chem. Soc. Jpn* **2004**, *77*, 59−72.

(29) Wei, N.; Murthy, N. N.; Chen, Q.; Zubieta, J.; Karlin, K. D. *Inorg. Chem.* **1994**, *33*, 1953−1965.

(30) Lucchese, B.; Humphreys, K. J.; Lee, D.-H.; Incarvito, C. D.; Sommer, R. D.; Rheingold, A. L.; Karlin, K. D. *Inorg. Chem.* **2004**, *43*, 5987−5998.

insights into the effects of ligands on the redox chemistry of copper(I) complexes with respect to an understanding of the carbon−halogen bond activation mechanism by these ligand-copper(I) complexes. The results reported herein may also provide mechanistic insight into the initiation process for atom transfer radical polymerization (ATRP) of olefins mediated by alkyl halides and copper(I) complexes.[31,32]

## Experimental Section

**General Methods.** All chemicals used in this study, except the ligands and the copper(I) complexes, were commercial products of the highest available purity and were further purified by standard methods, if necessary.[33] The ligands and the copper(I) complexes were prepared according to reported methods.[13,17,34,35] FT-IR spectra were recorded on a Shimadzu FTIR-8200PC, and UV−visible spectra were taken on a Hewlett-Packard 8453 photodiode array spectrophotometer equipped with a HP 89090A thermostated cell holder or a Unisoku cryostat cell holder USP-203. $^1$H NMR spectra were recorded on a JEOL FT-NMR Lambda 300WB or a JEOL FT-NMR GX-400 spectrometer. Mass spectra were recorded on a JEOL JMS-700T Tandem MS-station mass spectrometer. ESI-MS (electrospray ionization mass spectra) measurements were performed on a PE SCIEX API 150EX spectrometer. Cyclic voltammetry measurements were performed on an ALS 630 electrochemical analyzer in deaerated acetone containing 0.10 M $NBu_4ClO_4$ as supporting electrolyte. The Pt working electrodes (BAS) were polished with BAS polishing alumina suspension and rinsed with acetone before use. The counter electrode was a platinum wire. A silver pseudo reference electrode was employed, and electrochemical potentials were determined using the ferrocene/ferricenium (Fc/$Fc^+$) couple as a reference. All electrochemical measurements were carried out at 25 °C under an atmospheric pressure of Ar in a glovebox (DBO-1KP, Miwa Co. Ltd.).

**Product Analysis.** Typically, the copper(I) complex (0.02 mmol) was dissolved into deaerated acetone (5 mL) under anaerobic conditions. A benzyl halide (0.20 mmol) was then added to this solution, and the resulting mixture was stirred for 4 h at an appropriate temperature (see text). After removal of the solvent by evaporation, 15% $NH_4OH$ aqueous solution (10 mL) was added to the residue, and organic products were extracted by $CHCl_3$ (5 mL × 3). After drying over $K_2CO_3$, concentration of the solvent gave an organic materials, in which formation of the C−C coupled dimer product was confirmed by comparing the ESI-MS and $^1$H NMR to those of the authentic sample. The yield of the C−C coupling product was determined by $^1$H NMR spectroscopy using $CHCl_2$-$CHCl_2$ as an internal standard.

**Kinetic Measurements.** Typically, the reaction of benzyl halide (20−250 mM) and the copper(I) complex (2.0 mM) in acetone was followed by monitoring the increase of absorption in the visible region due to the d−d band of the copper(II)−halide product. The reaction obeyed a second-order rate law, and the second-order rate constants were determined from a standard plot of $(A_0 - A)/\{(A - A_\infty)[\mathrm{LCu}]_0\}$ against time, as shown in the inset of Figure 1.

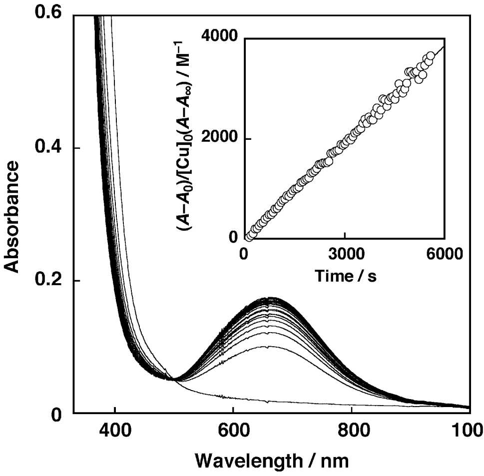


**Figure 1.** Spectral change of the reaction between $[\mathrm{Cu^I}(^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}})]\mathrm{ClO_4}$ ($2.0 \times 10^{-3}$ M) and benzyl chloride (0.084 M) in acetone at 50 °C. Inset: second-order plot based on the absorption change at 660 nm.

## Results

**Products and Kinetics**. As in the case of TMPA ligand system reported by Karlin et al.,[27] the reaction of copper(I) complex with short-armed tridentate ligand, $[\mathrm{Cu^I}(^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}})]\mathrm{ClO_4}$[17] (0.02 mmol) [$^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}}$; (2-pyridyl)methylamine tridentate ligand with phenethyl substituent (R = Phe; $-CH_2CH_2Ph$); see Chart 1], and benzyl chloride ($^{\mathrm{H}}$BnCl) (0.2 mmol) proceeded smoothly in acetone at 50 °C to give the corresponding C−C coupling dimer, 1,2-diphenylethane, in a 67% yield based on the copper(I) complex (the yield was corrected by doubling the isolated yield of the C−C coupling dimer since the molar ratio of the copper(I) complex and the dimer product is 2:1; see eq 1). In this reaction, the copper(I) complex was quantitatively converted into the corresponding copper(II)−chloride complex, $[\mathrm{Cu^{II}}(^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}})\mathrm{Cl}]\mathrm{ClO_4}$.[17]

Figure 1 shows spectral changes observed for the reaction, where a characteristic absorption band at 660 nm due to a ligand field transition of the copper(II)−chloride complex gradually increases as the reaction proceeds. Notably, the time course of the absorption change at 660 nm could be fitted by a second-order rate law equation even in the presence of a large excess of $^{\mathrm{H}}$BnCl (pseudo-first-order conditions), and the second-order rate constant ($k_{\mathrm{obs}}$) was obtained from the slope of the line from the second-order plot (inset of Figure 1). This second-order dependence of this reaction has been confirmed by the result that the second-order rate constants ($k_{\mathrm{obs}}$) obtained at various initial concentrations of $[\mathrm{Cu^I}(^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym}})]\mathrm{ClO_4}$ were inversely proportional to the initial concentration of $[\mathrm{Cu^I}(^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym}})]\mathrm{ClO_4}$, as expected from the equation for a second-order plot: $(A_0 - A)/\{(A - A_\infty)[\mathrm{Cu}]_0\} = k_{\mathrm{obs}}t$. Furthermore, the second-order rate constant ($k_{\mathrm{obs}}$) also exhibited a second-order dependence on $^{\mathrm{H}}$BnCl concentration (Figure 2). Thus, the kinetic equation for the reaction can be summarized as rate $= k[\mathrm{Cu}]^2[^{\mathrm{H}}\mathrm{BnCl}]^2$, where $k$ is an apparent fourth-order rate constant.

**Substituent Effects of the Substrates.** The reaction of a series of *p*-substituted benzyl chlorides ($^{\mathrm{Y}}$BnCl; Y = OMe, *t*-Bu, Me, H, F, Cl, $NO_2$) and $[\mathrm{Cu^I}(^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}})]\mathrm{ClO_4}$ was also

---

(31) Patten, T. E.; Matyjaszewski, K. *Acc. Chem. Res.* **1999**, *32*, 895−903.

(32) (a) Matyjaszewski, K.; Xia, J. H. *Chem. Rev.* **2001**, *101*, 2921−2990. (b) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689−3745.

(33) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, U.K., 1996.

(34) Karlin, K. D.; Sherman, S. E. *Inorg. Chim. Acta* **1982**, *65*, L39-L40.

(35) Jacobson, R. R.; Tyeklár, Z.; Farooq, A.; Karlin, K. D.; Liu, S.; Zubieta, J. *J. Am. Chem. Soc.* **1988**, *110*, 3690−3692.

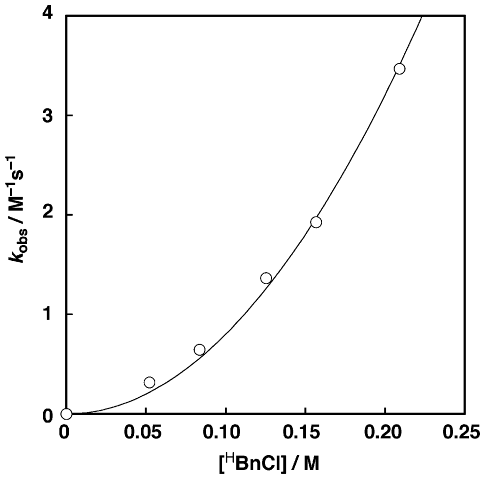


**Figure 2.** Plot of $k_{obs}$ vs [$^{H}$BnCl] for the reaction of benzyl chloride and [Cu$^{I}$($^{Phe}$L$^{Pym2}$)]ClO$_4$ in acetone at 50 °C.

**Table 1.** Yields of C−C Coupling Dimer and the Apparent Fourth-Order Rate Constants *k* for the Reactions of *p*-Substituted Benzyl Chlorides ($^{Y}$BnCl) and [Cu$^{I}$($^{Phe}$L$^{Pym2}$)]ClO$_4$ or [Cu$^{I}$(TMPA)(CH$_3$CN)]ClO$_4$ in Acetone

| | [Cu$^{I}$($^{Phe}$L$^{Pym2}$)]ClO$_4$ | | [Cu$^{I}$(TMPA)(CH$_3$CN)]ClO$_4$ | |
|---|---|---|---|---|
| *p*-Y | yield/%$^{a}$ | *k*/M$^{-3}$ s$^{-1}$ $^{a}$ | yield/%$^{b}$ | *k*/M$^{-3}$ s$^{-1}$ $^{c}$ |
| OMe | 39 | *d* | 74 | 8.8 ± 0.2 |
| *t*-Bu | 77 | 51.4 ± 2.4 | 77 | 44.6 ± 2.0 |
| Me | 67 | 43.2 ± 2.6 | 89 | 65.5 ± 2.9 |
| H | 67 | 80.2 ± 1.5 | 94 | 44.4 ± 2.2 |
| F | 69 | 69.0 ± 2.5 | 93 | 46.4 ± 4.0 |
| Cl | 72 | 153 ± 3.0 | 95 | 404 ± 17 |
| NO$_2$ | 74 | 2370 ± 66 | 97 | 57500 ± 930 |

$^{a}$ At 50 °C. $^{b}$ At 20 °C. $^{c}$ At −80 °C. $^{d}$ Too slow to be determined.

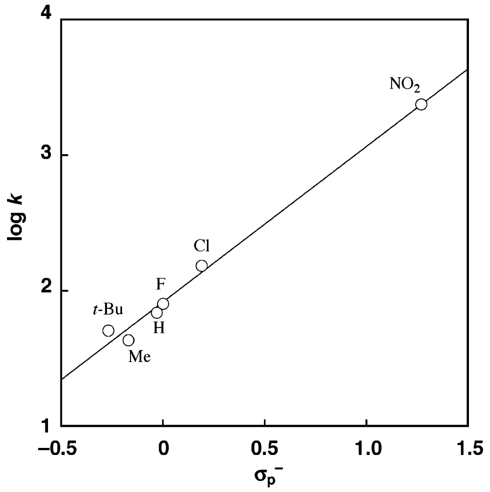


**Figure 3.** Hammett plot for the reaction of *p*-substituents benzyl chloride by [Cu$^{I}$($^{Phe}$L$^{Pym2}$)]ClO$_4$ in acetone at 50 °C.

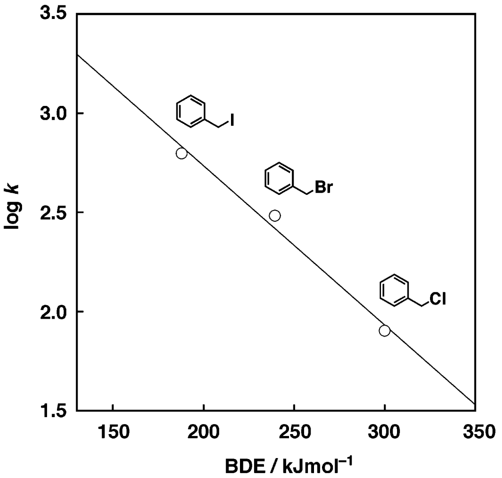


**Figure 4.** Plot of log *k* vs BDE of the carbon−halogen bond of the substrates for the reaction of $^{H}$BnX (X = Cl, Br, I) and [Cu$^{I}$($^{Phe}$L$^{Pym2}$)]ClO$_4$ in acetone at 50 °C.

examined under the same experimental conditions (Table 1). In all cases, the corresponding C−C coupling dimer products were obtained in fairly good yields, and the reaction obeyed second-order kinetics with respect to both the copper complex and the substrate, thus also obeying the kinetic equation, rate = $k$[Cu]$^2$[$^{R}$BnCl]$^2$. The apparent fourth-order rate constants were obtained in the same manner, and they are listed in Table 1. It is obvious that the reaction rate increases as the electron-withdrawing nature of the *p*-substituent (Y) increases, and the Hammett plot of log *k* vs $\sigma_p^-$ [36] gave a linear correlation with a positive slope ($\rho$ = 1.1) as shown in Figure 3. Furthermore, the reactivity of benzyl halides ($^{H}$BnX) increases in the order of Cl < Br < I, and the rate constants exhibit a linear correlation with the bond dissociation energy (BDE)[37] of the carbon−halogen bond of the substrates, as demonstrated by the plot given in Figure 4. The electronic effects of the *p*-substituents as well as the effect of BDE on the reaction rates are discussed below.

**Ligand Effects.** The reactivity of copper(I) complexes with other ligands shown in Chart 1 has also been examined in the reaction with $^{H}$BnCl at 50 °C in acetone. Interestingly enough, the reaction of [Cu$^{I}$(TMPA)(CH$_3$CN)]ClO$_4$ was extremely fast (completed within 1 s at 50 °C), whereas the copper(I) complexes with $^{Phe}$L$^{MePym2}$, $^{Phe}$L$^{Pye2}$ (R = phenethyl; see Chart 1), and TEPA exhibited virtually no reactivity. Thus, the supporting ligands caused dramatically different differential affects on the reactivity of copper(I) toward benzyl chloride.

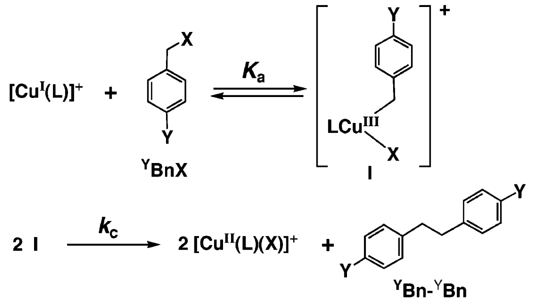
Since the reaction of [Cu$^{I}$(TMPA)(CH$_3$CN)]ClO$_4$ and $^{H}$BnCl was too fast to be followed at 50 °C, kinetic analysis of the reaction was performed at −80 °C. As in the case of [Cu$^{I}$($^{Phe}$L$^{Pym2}$)]ClO$_4$, the reaction obeyed second-order kinetics with respect to both the copper complex (see Supporting Information, Figure S1) and $^{H}$BnCl (Figure S2). Yields of the dimer products and the apparent fourth-order rate constants for the reactions of a series of $^{Y}$BnCl (Y = OMe, *t*-Bu, Me, H, F, Cl, NO$_2$) are also listed in Table 1. In this case as well, the reaction rate increases as the electron-withdrawing nature of the *p*-substituents increases, and the Hammett plot of log *k* vs $\sigma_p^-$ [36] also gave a linear correlation with a positive slope of $\rho$ = 2.3 (Figure S3). The similar kinetic behavior of the [Cu$^{I}$(TMPA)(CH$_3$CN)]ClO$_4$ and [Cu$^{I}$($^{Phe}$L$^{Pym2}$)]ClO$_4$ systems clearly suggests that the reaction mechanisms of both systems are essentially the same, even though the reaction rates vary significantly.

---

(36) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(37) Verevkin, S. P.; Krasnykh, E. L.; Wright, J. S. *Phys. Chem. Chem. Phys.* **2003**, *5*, 2605−2611.

**Scheme 1**



## Discussion

On the basis of the kinetic results described above, we propose a mechanism for the C−C coupling reaction shown in Scheme 1. Oxidative addition of the copper(I) complex to the C−X bond of substrate will afford a copper(III) organometallic intermediate **I**. Then, a bimolecular reaction of intermediate **I** takes place to give the C−C coupled dimer and the copper(II)−halide complex as products.

From this mechanism is derived the following kinetic equation:

$$\text{rate} = \frac{k_c K_a^{\,2}[^{Y}\mathrm{BnX}]^2[\mathrm{Cu}]_T^{\,2}}{(1 + K_a[^{Y}\mathrm{BnX}])^2} \tag{2}$$

Since the reaction is second-order with respect to both the copper complex (Figure 1) and the substrate (Figure 2), the $K_a[^{Y}\mathrm{BnX}]$ term must be much smaller than unity ($K_a[^{Y}\mathrm{BnX}] \ll 1$) under the present experimental conditions. As such, the kinetic equation can be simplified as the following:

$$\text{rate} = k_c K_a^{\,2}[^{Y}\mathrm{BnX}]^2[\mathrm{Cu}]_T^{\,2} \tag{3}$$

Here $k_c K_a^2$ corresponds to the apparent fourth-order rate constant $k$. Although the $k_c$ and $K_a$ processes could not be evaluated separately, the linear correlation between the rate constant and BDE (Figure 4) can be simply attributed to the oxidative addition process ($K_a$). Namely, the oxidative addition of copper(I) into the C−X bond of the substrates may be enhanced as the C−X bond becomes weaker.

With respect to the electronic effects of *p*-substituents (Y) of $^{Y}$BnCl, the electron-withdrawing substituents may stabilize the intermediate **I** since its benzylic carbon has a carboanionic ($\delta^-$) character. Thus, the formation of intermediate **I** ($K_a$ process) would be accelerated by the electron-withdrawing substituents, being consistent with the positive slope of the Hammett plot (Figure 3 and Figure S3). On the other hand, the C−C coupling process ($k_c$) may be more like a radical character in nature (the transition state of the C−C coupling reaction is discussed below). Thus, *p*-substituent effects on the $k_c$ process might be smaller than those for the $K_a$ process.

Inspection of the oxidation potential and dioxygen reactivity of the copper(I) complexes gave us a clue to understand the remarkable effects of the supporting ligands in the present C−X bond activation chemistry (see Table 2). With regard to the oxidation potential ($E_{ox}$; i.e., the measure of the $\mathrm{Cu^I/Cu^{II}}$ redox couple) of the copper(I) complexes, significant differences exist, with values ranging from −430 to +120 mV vs Fc/Fc$^+$ (Table 2). Apparently, the copper(I) complexes with large negative $E_{ox}$ values, $[\mathrm{Cu^I(TMPA)(CH_3CN)]ClO_4}$ and $[\mathrm{Cu^I(^{Phe}L^{Pym2})]ClO_4}$, react with benzyl halides, whereas the copper(I) complexes with the higher $E_{ox}$ value do not. The lower oxidation potentials of $[\mathrm{Cu^I(TMPA)(CH_3CN)]ClO_4}$ and $[\mathrm{Cu^I(^{Phe}L^{Pym2})]ClO_4}$ indicate that their higher oxidation states ($\mathrm{Cu^{II}}$ and $\mathrm{Cu^{III}}$) are more stabilized than those of the others, due to the overall stronger donating ability of the ligands (TMPA and $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}}$).[38] Thus, the observed reactivity of $[\mathrm{Cu^I(TMPA)(CH_3CN)]ClO_4}$ and $[\mathrm{Cu^I(^{Phe}L^{Pym2})]ClO_4}$ toward $^{Y}$BnX can be attributed in part to ligand stabilization of the copper(III)-intermediate **I**, enhancing its formation process ($K_a$ process in Scheme 1). In other words, the ligands with lower donor ability such as $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{MePym2}}$, $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pye2}}$, and TEPA would unlikely support such a high oxidation state proposed for intermediate **I**, resulting in no reactivity toward $^{Y}$BnX. In support of this notion, the reactivity of $[\mathrm{Cu^I(TMPA)(CH_3CN)]ClO_4}$ and $[\mathrm{Cu^I(^{Phe}L^{Pym2})]ClO_4}$ toward $O_2$ (which involves a redox process) is significantly greater (in rate) than that of the other complexes (compare the $k_{obs}$ values in Table 2), and $[\mathrm{Cu^I(^{Phe}L^{Pym2})]ClO_4}$ provides the high-valent bis($\mu$-oxo)dicopper(III) complex **C** in contrast to the case of $[\mathrm{Cu^I(^{Phe}L^{MePym2})]ClO_4}$ and $[\mathrm{Cu^I(^{Phe}L^{Pye2})]ClO_4}$ which produce the side-on peroxo dicopper(II) complex **B** (the difference in structure of the $\mathrm{Cu_2O_2}$ complex derived from $[\mathrm{Cu^I(TMPA)(CH_3CN)]ClO_4}$ from those of the others can be attributed to the difference in ligand denticity).[2]

**Table 2.** Oxidation Potential ($E_{ox}$) and $O_2$ Reactivity (Structure of the $\mathrm{Cu_2O_2}$ Complex Formed and Its Formation Rate Constant) of the Copper(I) Complexes

| ligand | $E_{ox}$/V vs Fc/Fc$^+$ [a] | $\mathrm{Cu_2O_2}$ complex | $O_2$ reactivity $k_{obs}/\mathrm{M^{-1}\,s^{-1}}$ |
|---|---|---|---|
| TMPA | −0.43 (−0.06) | **A**[b] | $(1.0 \pm 0.2) \times 10^{5}$ [c] |
| $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}}$ | −0.30 (+0.07) | **C**[d] | $(5.9 \pm 0.02) \times 10^{4}$ [d,e] |
| $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{MePym2}}$ | −0.040 (+0.33) | **B**[f] | 70 ± 0.4[f,g] |
| $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pye2}}$ | 0 (+0.37) | **B**[h] | 2.0 ± 0.1[h,i] |
| TEPA | +0.12 (+0.49) | | NR[j] |

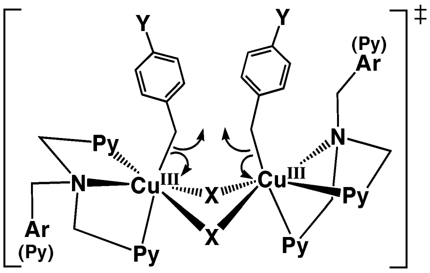
[a] In acetone containing 0.1 M tetrabutylammonium perchlorate (TBAP); scan rate 50 ~100 mV s$^{-1}$ at 25 °C. $E_{ox}$ values vs SCE are shown in parentheses. [b] Reference 7. [c] At −90 °C in THF; ref 22. [d] Reference 17. [e] At −94 °C in acetone. [f] Reference 19. [g] At −94 °C in acetone. [h] Reference 13. [i] At −80 °C in THF. [j] Reference 9.

Although no direct evidence concerning an intermediate or nature of the transition state associated with the $k_c$ process is available, our knowledge that a bis($\mu$-oxo)dicopper(III) complex **C** forms with the tridentate ligand $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}}$ lets us propose a transition state for the C−C coupling reaction as shown in Scheme 2. The second-order dependence both on the copper complex and the substrate indicates that two molecules of that intermediate **I** (Scheme 1) should collapse together, where halogen ions (X) may act as the bridging ligands to connect the two copper ions. The $\mathrm{Cu_2X_2}$ core structure resembles the $\mathrm{Cu_2O_2}$ core structure in bis($\mu$-oxo)dicopper(III) complex **C**, and halides are well-known bridg-

---

(38) Stabilization of the higher oxidation state of intermediate **I** could also be attributed to the coordination/geometry/denticity overall effects of the ligands.

**Scheme 2**



ing ligands.[39] Although the copper ion is drawn as 6-coordinated in Scheme 2, the coordination number of copper could be 5. In this case, one of the pyridine nuclei of $^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}}$ would detach from the copper center, Scheme 2.

In the case of the tetradentate TMPA ligand system, at least one pyridine donor should be free from metal coordination (Ar = Py in the TMPA system). In fact, one of the pyridine donors in the starting copper(I) complex $[\mathrm{Cu^I}(\mathrm{TMPA})(\mathrm{CH_3CN})]\mathrm{ClO_4}$ does not coordinate to the metal ion.[7,35] Then, the extremely high reactivity of the TMPA tetradentate ligand system can be interpreted as follows. The uncoordinated Py group may attack the copper center from the backside of Cu−C bond, which induces the Cu−C bond cleavage to enhance the C−C bond formation (a so-called push effect). Thus, the presence of the ligand TMPA accelerates not only the $K_a$ process by stabilizing the high-valent copper(III) oxidation state of intermediate **I** but also the $k_c$ process by enhancing the Cu−C bond breaking. In support of TMPA at least transiently supporting a copper(III) oxidation state, we note that a bis($\mu$-oxo)dicopper(III) complex is supported by a 6-methyl-substituted TMPA ligand.[40] It is for these reasons that we suggest why the copper(I) complex of TMPA exhibits such a high reactivity in the C−X cleavage and C−C bond formation reactions.

In atom transfer radical polymerization (ATRP) of olefins mediated by alkyl halides (RX) and copper(I) complexes ($\mathrm{Cu^IL}$; L = ligand), the initiation process involves a reaction of RX and $\mathrm{Cu^IL}$, generating an alkyl radical species $\mathrm{R^\bullet}$, which adds to the olefin to initiate the radical chain polymerization reaction. It has been proposed that the initiation process involves electron transfer from $\mathrm{Cu^IL}$ to RX, producing a radical anion intermediate $\mathrm{RX^{\bullet-}}$ from which the organic radical $\mathrm{R^\bullet}$ is generated by homolytic cleavage of the carbon−halogen bond of $\mathrm{RX^{\bullet-}}$. Eventual formation of the free organic radical $\mathrm{R^\bullet}$ has been well documented by several lines of experimental evidence.[31,32]

In the present C−C coupling reaction, however, a similar electron-transfer initiated reaction between the copper(I) complex and $^{\mathrm{Y}}\mathrm{BnX}$ is unlikely, since this process would be energetically unfavorable; the reduction peak potential of $^{\mathrm{Y}}$-BnX (cf.: $^{\mathrm{H}}\mathrm{BnCl}$, −2.24 V vs SCE; $^{\mathrm{H}}\mathrm{BnBr}$, −1.74 V vs SCE; scan rate 0.1 V $\mathrm{s^{-1}}$ in $\mathrm{CH_3CN}$)[41] is significantly negative as compared to the oxidation potential of the copper(I) complexes ($[\mathrm{Cu^I}(\mathrm{TMPA})(\mathrm{CH_3CN})]\mathrm{ClO_4}$, −0.06 V vs SCE; $[\mathrm{Cu^I}(^{\mathrm{Phe}}\mathrm{L}^{\mathrm{Pym2}})]\mathrm{ClO_4}$, +0.07 V vs SCE; see Table 2). If such an electron-transfer occurred, it should be the rate-determining process. However, the second-order dependence both on the copper(I) complex and the substrate is inconsistent with this mechanism, since this should obey first-order kinetics with respect to both the copper(I) complex and the substrate. Namely, once the rate-determining electron transfer occurred, the $^{\mathrm{Y}}\mathrm{Bn^\bullet}$ alkyl radical generated would rapidly collapse to give the C−C coupling dimer product. Thus, to explain the kinetic data observed for the present RX reductive coupling chemistry, there must be an association between the copper complex and the substrate such as intermediate **I**, which undergoes a bimolecular reaction to give the final products (Scheme 1). Further studies are being undertaken to obtain information concerning intermediate **I**.

**Acknowledgment.** This work was financially supported in part by Grants-in-Aid for Scientific Research (No. 15350105) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and by Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists (to T.O). K.D.K. acknowledges the U.S. National Science Foundation for support through a Collaborative Research Activities in Environmental Molecular Science (CRAEMS) research grant.

**Supporting Information Available:** Kinetic results for the reaction of $[\mathrm{Cu^I}(\mathrm{TMPA})(\mathrm{CH_3CN})]\mathrm{ClO_4}$. This material is available free of charge via the Internet at http://pubs.acs.org.

IC048902E

---

(39) Hathaway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, 1987; pp 533−774.

(40) Mizuno, M.; Hayashi, H.; Fujinami, S.; Furutachi, H.; Nagatomo, S.; Otake, S.; Uozumi, K.; Suzuki, M.; Kitagawa, T. *Inorg. Chem.* **2003**, *42*, 8534−8544.

(41) Andrieux, C. P.; Legorande, A.; Savéant, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 6892−6904.