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The Role of Chelating Diamine Ligands in the Goldberg Reaction: A Kinetic Study on the Copper-Catalyzed Amidation of Aryl lodides

Eric R. Strieter,[†] Donna G. Blackmond,[‡] and Stephen L. Buchwald*,[†]

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, and the Department of Chemistry, Imperial College, London SW7 2AZ, U.K.

Received January 8, 2005; E-mail: sbuchwal@mit.edu

Copper-catalyzed C–N bond formation has long been a practical and efficient method for the construction of aryl C–N bonds in both academic and industrial settings.¹ Recently we reported on an enhanced version of the Goldberg reaction,² the copper-catalyzed amidation of aryl and heteroaryl halides, using CuI and chelating 1,2-diamines in combination with K₃PO₄, K₂CO₃, or Cs₂CO₃.³ Although this process displays increased activity and substrate scope relative to its predecessors, the development of improved catalysts hinges on our ability to understand the catalytic events. Herein we report on a mechanistic study identifying the role of the diamine in preventing multiple ligation of the amide^{4,5} and also demonstrate that a copper(I) amidate can serve as a potential intermediate during the *N*-arylation process.⁶

The reaction between 3,5-dimethyliodobenzene (1) and 2-pyrrolidinone (2) was selected for the kinetic studies due to its efficiency (99% yield after 2 h, eq 1). The reactions were continuously monitored in a reaction calorimeter (Omnical SuperCRC) as previously described.^{7,8} Since our initial studies focused on determining the precise role of the diamine in this reaction, the reaction rate was examined as a function of [3]. As shown in Figure 1, a nonlinear relationship between [3] and the reaction rate was observed over a 19-fold change in [3]. The observation that complete dissolution of the copper(I) salt occurs in a mixture containing 3 and CuI in a 1:1 ratio precludes an explanation for the saturation behavior based on a change in solubility of the active copper(I) species.⁶⁶ A firstorder dependence on [copper]_{total} in reactions with Cu(I):3 ratios of both 1:2 and 1:10 also rules out catalyst decomposition.¹⁰



A third possibility for the saturation dependence on [3] suggests that multiple ligation of the amide leading to an inactive copper species may be prevented at high concentrations of $3^{3c,9}$ The mechanism shown in Scheme 1 proposes that the intermediate copper(I) amidate (B) is formed either through amide coordination to A followed by deprotonation or through diamine association and subsequent amide dissociation from C. Once formed, B reacts with the aryl iodide, affording the desired *N*-arylated amide. The corresponding rate expression is given by eq 2 (where quasiequilibria are assumed: $K_1 = k_1/k_{-1}$ and $K_2 = k_2/k_{-2}$). This is consistent with the kinetic data in Figure 1, showing saturation kinetics in [3] with all other concentrations held constant.¹¹

Evaluating the kinetic dependence on [Amide] provides additional support for this model in the form of limiting cases of the rate expression given in eq 2.¹² Specifically, the first-order diamine



Figure 1. Reaction rate at 50% conversion of 1 vs [3] in the N-arylation of 2 (0.8 M) with 1 (0.4 M) using [CuI] (0.02 M).

Scheme 1. Proposed Mechanism



dependence at low [3] suggests that under these conditions the resting state of the catalyst is the multiply amide-ligated species **C**. Increasing concentrations of the diamine 3 drive the reaction back to intermediate **B** in equilibrium with **A**. Thus, increasing concentrations of diamine increases the reaction rate, while increasing amide concentrations should suppress it. This results in the limiting case of the rate expression of eq 2 shown in eqs 3a and 3b. The straight-line relationship between the function rate/[ArI] and 1/[Amide] provided by eq 3b is borne out in Figure 2a, where three experiments performed at different [Amide] converge into



Figure 2. Reaction rate dependence on [amide]. (a) rate/[ArI] vs 1/[Amide] at low [**3**] (10 mol % **3**, 5 mol % CuI). Reaction conditions: $[1]_o = 0.4$ M, $(\bigcirc) [2]_o = 0.9$ M, $(\diamondsuit) [2]_o = 0.7$ M, $(\square) [2]_o = 0.6$ M. (b) rate/[Amide] vs [ArI] at high [**3**] (70 mol % **3**, 5 mol % CuI). Reaction conditions: $(\bigcirc) [2]_o = 0.9$ M, $[1]_o = 0.4$ M, $(\diamondsuit) [2]_o = 1.0$ M, $[1]_o = 0.6$ M, $(\square) [2]_o = 0.7$, $[1]_o = 0.6$ M.

[†] Massachusetts Institute of Technology.

the same straight-line relationship with slope equal to K'. These data confirm the inverse dependence on [Amide] at low [3]. By contrast, under conditions of high [3], Figure 2b reveals that a straight-line relationship is observed between the function rate/ [Amide] versus [ArI], suggesting the limiting form of eq 2 shown in eq 4b. This implies that, under high [3], K_1 [Amide] $\ll 1$ and the resting state of the catalyst shifts to species A, giving first-order kinetics in both [ArI] and [Amide] and zero-order kinetics in [3].

$$\frac{k_{\text{act}}K_1K_2[\text{Cu}]_t[\text{ArI}][\text{Amide}][\text{Diamine}]}{K_1[\text{Amide}]^2 + K_2[\text{Diamine}] + K_1K_2[\text{Amide}][\text{Diamine}]}$$
(2)

low [Diamine]:

rate =

$$rate = \frac{k_{act}K_1K_2[Cu]_t[ArI][Diamine]}{[Amide]}$$
(3a)

or
$$\frac{\text{rate}}{[\text{ArI}]} = K' \cdot \frac{1}{[\text{Amide}]}$$
 $K' = k_{\text{act}} K_2 [\text{Cu}]_t [\text{Diamine}]$ (3b)

high [Diamine]:

rate =
$$\frac{k_{act}K_1[Cu]_t[ArI][Amide]}{1 + K_1[Amide]} \approx k_{act}K_1[Cu]_t[ArI][Amide]$$

or
$$\frac{\text{rate}}{[\text{Amide}]} = K'' \cdot [\text{ArI}] \quad K'' = k_{\text{act}} K_1 [\text{Cu}]_t \quad (4b)$$

We sought to evaluate further the potential intermediacy of a copper(I) amidate complex (**B** in Scheme 1) now that this species was substantiated through kinetic analysis. To accomplish this goal, copper(I) amidate 5 was synthesized by mixing 2 with mesitylcopper at room temperature in toluene. As evidenced by the broadened resonances in the ¹H NMR, 5 exists as multiple oligomers in solution, which is consistent with the tendency of most copper-(I) complexes to exist as aggregates.¹³ Upon addition of diamine **3** to the solution containing 5, however, a single species results as indicated by the sharpened resonances of the copper(I) amidate protons. Most significantly, the addition of aryl iodide 1 to this mixture of 5 and 3 at 0 °C resulted in complete conversion of the copper(I) amidate, affording a $t_{1/2}$ of 3.1 min (eq 5).¹⁴ This experiment establishes both the chemical and kinetic competency of a copper(I) amidate intermediate.



In summary, the kinetic data suggest that the diamine serves to prevent multiple ligation of the amide. Higher concentrations of the diamine allow the activation of the aryl iodide to become the

rate-limiting step. At low concentrations of diamine, however, the catalyst resides as a multiply ligated species, which requires the dissociation of an amide through diamine coordination to generate the active copper(I) amidate, an intermediate that has been demonstrated to be both chemically and kinetically competent for the N-arylation. These results show that both the diamine and the amide play vital roles in the rate at which the N-arylation occurs.

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Note Added after ASAP Publication: In the version published on the Internet February 26, 2005, there were production errors in eqs 3a, 3b, and 4a. In the final version published March 1, 2005, and in the print version, these equations are correct.

Supporting Information Available: Experimental procedures, kinetic data, and reaction rate derivation (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

- For reviews, see: (a) Lindley, J. Tetrahedron 1984, 40, 1433. (b) Ley, S.
 V.; Thomas, A. W. Angew. Chem., Int. Ed. 2003, 42, 5400. (c) Kunz, K.;
 Scholz, U.; Ganzer, D. Synlett 2003, 2428. (d) Beletskaya, I. P.;
 Cheprakov, A. V. Coord. Chem. Rev. 2004, 248, 2337.
- (2) (a) Goldberg, I. Ber. Disch. Chem. Ges. 1906, 39, 1691. (b) Sugahara, M.; Ukita, T. Chem. Pharm. Bull. 1997, 45, 719.
- (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. J. Am. Chem. Soc. 2001, 123, 7727. (b) Wolter, M.; Klapars, A.; Buchwald, S. L. Org. Lett. 2001, 3, 3803. (c) Klapars, A.; Huang, X.; Buchwald, S. L. J. Am. (3)Chem. Soc. 2002, 124, 7421.
- (4) For examples where increasing the [ligand] inhibits copper-promoted reactions, see: (a) Bacon, R. G. R.; Hill, H. A. O. J. Chem. Soc. 1964, 1097. (b) Rusonik, I.; Cohen, H.; Meyerstein, D. J. Chem. Soc., Dalton Trans. 2003, 2024. For examples of ligand-accelerated copper-catalyzed reactions, see: (c) Goodbrand, H. B.; Hu, N. X. J. Org. Chem. 1999, 64, 670. (d) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. Tetrahedron Lett. J. J. Am. Chem. Soc. 2000, 122, 5043.
- (5) One explanation for the activity of catalysts based on 1,2-diamines is that they increase the oxidation potential of copper(I), thus facilitating the activation of the aryl halide; see ref 4b. (6) (a) Yamamoto, T.; Ehara, Y.; Kubota, M.; Yamamoto, A. *Bull. Chem.*
- Soc. Jpn. 1980, 53, 1299. (b) Paine, A. J. J. Am. Chem. Soc. 1987, 109 (c) Blue, E. D.; Davis, A.; Conner, D.; Gunnoe, T. B.; Boyle, P. D.; White, P. S. J. Am. Chem. Soc. 2003, 125, 9435.
 (7) (a) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. J. Am. Chem. Soc. 2002, 124, 14104. (b) Nielsen, L. P. C.; Stevenson, C. M. Chem. Soc. 2002, 124, 14104.
- P.; Blackmond, D. G.; Jacobsen, E. N. J. Am. Chem. Soc. 2004, 126, 1360.
- (8) The use of a heterogeneous inorganic base such as K₃PO₄ may limit the reaction rate due to mass transfer effects. However, using different stirring rates resulted in identical reaction rate profiles, thus ruling out the possibility of a mass transfer limited process.
 (9) Bacon, R. G. R.; Karim, A. J. J. Chem. Soc., Perkin Trans. 1 1973, 272.
- (10) See Supporting Information.
- (11) Figure 1 data at constant [ArI], [Cu]_T, and [Amide] simplify eq 2 to the form: rate = a[3]/(1 + b[3]), where a and b are adjustable parameters.
- (12) Reaction rate is independent of [base] at both low and high [3]. This is presumably due to saturation of the base in a nonpolar solvent, and thus, the [base] is treated as a constant. See Supporting Information for more details.
- (13) For the synthesis of copper(I) amides, see: (a) Tsuda, T.; Watanabe, K.; Miyata, K.; Yamamoto, H.; Saegusa, T. *Inorg. Chem.* **1981**, *20*, 2728. (b) Hope, H.; Power, P. P. *Inorg. Chem.* **1984**, *23*, 936. (c) Gamboratta, S.; Bracci, M.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. J. Chem. Soc., Dalton Trans. 1987, 1883
- (14) Arylation of 5 in the absence of 3 did not proceed at temperatures between 0 °C and 90 °C.

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