J|A|C|S
COMMUNICATIONS

What is the Rate of the $Csp^2{-}Csp^2$ Reductive Elimination Step? Revealing an Unusually Fast Ni-Catalyzed Negishi-Type Oxidative Coupling Reaction

Liqun Jin,[†] Hua Zhang,[†] Peng Li,[†] John R. Sowa, Jr.,[‡] and Aiwen Lei*,[†,§]

College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, P. R. China, Seton Hall University, Department of Chemistry and Biochemistry, South Orange, New Jersey 07079, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai, 200032, P. R. China

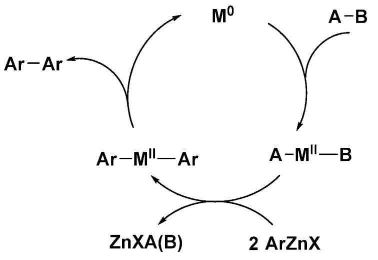
Received May 12, 2009; E-mail: aiwenlei@whu.edu.cn

Although reductive elimination has been known for over 40 years and is an essential step in coupling reactions,[1−6] within the catalytic cycle, there are very few quantitative kinetic studies of the $Csp^2{-}Csp^2$ reductive elimination.[7,8] Investigation of stoichiometric reactions of biaryl Ni, Pd, and Pt complexes reveals valuable insight into the reductive elimination step.[9−11] The rate constants of the reductive elimination of $Csp^2{-}Pd{-}Csp^2$ and $Csp^2{-}Pt{-}Csp^2$ systems have been measured to be in the range of 10^{-3} to 10^{-5} s^{-1}.[9,10] In sharp contrast, catalytic reactions for $Csp^2{-}Csp^2$ couplings appear to be much faster, as catalytic processes can occur at temperatures as low as −30 °C which indicates a much lower energy activation barrier.[12]

Collman et al. in 1987 discussed that the rates of many reductive elimination reactions are very difficult to obtain because they are so exothermic and the corresponding oxidative addition is unknown.[13] In fact, until today, there are still few bis-aryl Ni and Pd complexes that have been employed to study the reductive elimination step.[9−11,14] To obtain a quantitative measurement of reductive elimination, stoichiometric systems have to be carefully designed to provide meaningful data. For example, recently, the corresponding Pt complexes have been successfully investigated.[9] However, it is possible that these systems do not accurately reflect the reductive elimination rate in the catalytic cycle.[15]

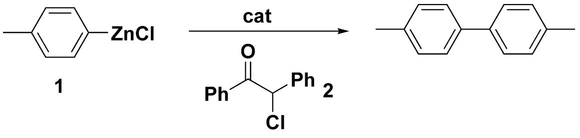
To gain an accurate measurement of the rate of $Csp^2{-}Csp^2$ reductive elimination within a catalytic reaction, it should be the rate-determining step.[8,16,17] In cross-coupling reactions, when aryl chlorides or aryl bromides are utilized as electrophiles, oxidative addition is usually the rate-determining step.[5,16] Although aryl iodides are known to react more rapidly, to our knowledge, reductive elimination has not been shown to be rate-limiting with these electrophiles. Thus, it is important to devise a new system that allows quantitative investigation of reductive elimination rates within the catalytic cycle.

Scheme 1. Proposed Mechanism for the Oxidative Coupling Reaction



Recently, we have been focusing on oxidative coupling reactions and were inspired to investigate the kinetics of $Csp^2{-}Csp^2$ coupling reactions (Scheme 1).[18−20] With the proper choice of oxidant A−B and organometallic reagents that rapidly undergo oxidative addition and transmetalation, reductive elimination might become a rate-determining step and, therefore, can be measured quantitatively. Herein, we report our efforts in the kinetic measurement of the $Csp^2{-}Csp^2$ reductive elimination step in a catalytic sequence occurring through a Ni-catalyzed Negishi-type oxidative coupling reaction.

The model system we have devised shown in eq 1 consisted of desyl chloride (2-chloro-1,2-diphenylethanone) **2** as the A−B type oxidant and aryl zinc **1**. Our initial studies began with reactions catalyzed by $Pd(OAc)_2$ at 20 and 0 °C. As shown in Figure 1, plots of [Ar−Ar] formation vs time gave straight lines which indicates that the reaction rate is independent of [**1**] and [**2**]. Since Ni-catalyzed coupling reactions are also known, we then investigated the kinetics with our newly devised model employing $Ni(acac)_2$ as the catalyst. To our surprise, these reactions were so fast that they went to completion within seconds at 20, 10, and even 0 °C (Figure 1). Thus, we further lowered the reaction temperature to −35 °C, so that we could obtain a significant number of data points. At this temperature, the reaction was completed within 6 min, and the kinetic plot was also a straight line. Again, this clearly shows that the reaction rate is independent of [**1**] and [**2**].[8,21]



(1)

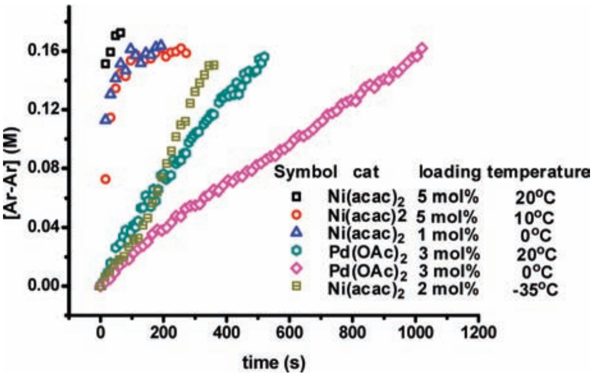


Figure 1. Reaction progress profiles for oxidative coupling reactions in the presence of different catalyst systems at varied temperatures with *in situ* IR.

[†] Wuhan University.
[‡] Seton Hall University.
[§] Chinese Academy of Sciences.

10.1021/ja903833u CCC: $40.75

The kinetic profiles in both Pd- and Ni-catalyzed oxidative coupling reactions show that the rates are independent of [**1**] and [**2**]. This indicates a zero-order kinetic behavior. With the catalytic cycle shown in Scheme 1, if either the oxidative addition or transmetalation step is the rate-determining step, the reaction rate will decrease as **1** or **2** is consumed, resulting in a first-order kinetic curve. If the reductive elimination is the slow step, the reaction rate will only depend on [Ar−Ni−Ar]. The rate will be independent of [**1**] and [**2**] and will show a zero-order kinetic curve. Thus, data in Figure 1 imply that the reductive elimination step in this oxidative coupling reaction might be the rate-determining step.

To confirm that the reductive elimination is indeed a rate-limiting step, it is necessary to perform the kinetic studies with different initial [**1**] and [**2**] (see Supporting Information Figure S1). All reactions exhibit zero-order kinetic plots and show identical rates. The results do indicate that the rate of this oxidative coupling is independent of [**1**] and [**2**] and that reductive elimination is the rate-limiting step. It is also noteworthy that the catalytic reaction is first-order in $Ni(acac)_2$ (see Supporting Information Figure S2) and the overlay of the same excess experiments suggests that catalyst deactivation does not occur (see Supporting Information Figure S1).[22]

Thus far, all evidence connects the zero-order kinetic behavior with reductive elimination as the rate-limiting step. However, another possibility exists. If the Ni species generated from the reductive elimination of Ar−Ni−Ar is different from the Ni species required for oxidative addition of **2**, and the rate-determining step is the transformation between these two species, then zero-order kinetics will also be observed. We define this transformation as the "black-box process".[23] To distinguish between the reductive elimination as the rate-limiting step or the "black-box process", reactions of arylzinc reagents bearing different functionalities were carried out (see Supporting Information Figure S3). The oxidative coupling reactions of *p*-MeOPhZnCl and *p*-ClPhZnCl were carried out at −10 °C in the presence of 0.2 mol % $Ni(acac)_2$, and different rates were observed (Table 1, entries 8 and 9). This excludes the possibility of the "black-box process" as the rate-limiting step. Hence, reductive elimination as the rate-determined step in this Ni-catalyzed oxidative coupling is unambiguously confirmed.

Table 1. Reductive Elimination Reaction Rate Constants of $Csp^2{-}Ni{-}Csp^2$ [a]

entry	ArZnX	T (°C)	*k* (s^{-1})	
1	*p*-MePhZnCl	0	3.5	
2	*p*-MePhZnCl	-10	2.4	$\Delta H^{\ddagger} = 9.7$ kcal mol^{-1},
3	*p*-MePhZnCl	-15	1.3	
4	*p*-MePhZnCl	-20	0.87	$\Delta S^{\ddagger} = 35$ J mol^{-1} K^{-1}
5	*p*-MePhZnCl	-25	0.67	
6	*p*-MePhZnCl	-35	0.23	
7	PhZnCl	-10	1.2	
8	*p*-MeOPhZnCl	-10	0.37	
9	*p*-ClPhZnCl	-10	1.6	

[a] For details of kinetic profiles, see Supporting Information.

Our model reaction provides an opportunity to quantitatively determine the rate and the Arrhenius parameters for the $Csp^2{-}Csp^2$ reductive elimination step. In Table 1, we have explored the kinetics of the reactions with different aryl zinc reagents and different temperatures. All of the reactions exhibit zero-order kinetics, and the rate constants for the reductive elimination range from 0.23 s^{-1} at −35 °C to 3.5 s^{-1} at 0 °C, which is ∼3−4 orders of magnitude greater than the reported values.[9]

For the Arrhenius parameters, plots of $\ln(k/T)$ vs $1/T$ (see Supporting Information Figure S4) for the reaction of *p*-MePhZnCl give a smooth linear relationship, allowing calculation of the activation energy in the oxidative coupling reaction. According to the Arrhenius equation, we obtain the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ ($\Delta H^{\ddagger} = 9.7$ kcal mol^{-1}, $\Delta S^{\ddagger} = 35$ J mol^{-1} K^{-1}). In addition, the positive $\Delta S^{\ddagger}$ value is consistent with reductive elimination as the rate-limiting step.

The remarkable feature of our results is that the system uniquely allows direct quantitative investigation of a $Csp^2{-}Csp^2$ reductive elimination within a catalytic cycle. Even at −35 °C, the rate constant of the reductive elimination of $Csp^2{-}Csp^2$ is 0.23 s^{-1}, which is an unusually fast reaction rate. **The value itself reveals the facile nature of $Csp^2{-}Csp^2$ reductive elimination process.** The novel and reliable oxidative coupling model allows us to gain an insight into the activation energy barrier and entropy of the reductive elimination, which derived from a living catalytic cycle. Moreover, it is also remarkable that this is a system without phosphine or nitrogen based ligands, and the small value of $\Delta H^{\ddagger}$ reveals that, for this particular reaction, fundamentally the reductive elimination step is an extremely facile process.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (20702040, 20832003) and the startup fund from Wuhan University.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet as http://pubs.acs.org.

References

(1) Singleton, D. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1967**, *89*, 6547–6555.
(2) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857–1867.
(3) Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031–1046.
(4) Ozawa, F. In *Fundamentals of Molecular Catalysis*; Kurosawa, H., Yamamoto, A., Eds.; Elsevier: New York, 2003; Vol. 3, pp 479–512.
(5) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734.
(6) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947.
(7) Amatore, C.; Jutand, A. *Organometallics* **1988**, *7*, 2203–2214, and references therein.
(8) Mathew, J. S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711–4722.
(9) Shekhar, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 13016–13027.
(10) Osakada, K.; Onodera, H.; Nishihara, Y. *Organometallics* **2005**, *24*, 190–192.
(11) Koizumi, T.-A.; Yamazaki, A.; Yamamoto, T. *Dalton Trans.* **2008**, 3949–3952.
(12) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844–3845.
(13) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and applications of organotransition metal chemistry*; University Science Books: Mill Valley, CA, 1987; p 323.
(14) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547–7560.
(15) Albeniz, A. C.; Espinet, P.; Martin-Ruiz, B. *Chem.—Eur. J.* **2001**, *7*, 2481–2489.
(16) Jordan, R. B. *Organometallics* **2007**, *26*, 4763–4770.
(17) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718–2725.
(18) Jin, L.; Zhao, Y.; Zhu, L.; Zhang, H.; Lei, A. *Adv. Synth. Catal.* **2009**, *351*, 630–634.
(19) Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 9429–9433.
(20) Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* **2006**, *128*, 15048–15049.
(21) Zhang, H.; Luo, X.; Wongkhan, K.; Duan, H.; Li, Q.; Zhu, L.; Wang, J.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. *Chem.—Eur. J.* **2009**, *15*, 3823–3829.
(22) Refer to the explanation of Donna Blackmond in *J. Org. Chem.* **2006**, *71*, 4711−4722.
(23) Because the black-box process does not involve substrates, if it is a rate-limiting step, zero-order kinetics will be observed. In addition, the reaction with different substrates will also occur at the same rate.

JA903833U