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Pincer Thioamide and Pincer Thioimide Palladium Complexes Catalyze Highly Efficient Negishi Coupling of Primary and Secondary Alkyl Zinc Reagents at Room Temperature

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Abstract: Pincer thioamide Pd^{II} complex **2** was prepared, and its reaction with cyclohexylzinc chloride yielded novel pincer thioimide Pd^{II} complex **3** besides Pd^{0} species. The structures of complexes **2** and **3** were confirmed by X-ray analysis. Both complexes are efficient catalysts for Negishi couplings involving primary and secondary alkyl zinc reagents bearing β-hydrogen atoms. At a concentration of 0.1–0.5 mol% both catalysts readily promoted reactions at room temperature or even at 0°C. The operational simplicity of these processes, in conjunction with the easy accessibility of both catalysts and substrates, promises synthetic utility of this new methodology. An experiment on a scale of 19.35 g carried out at very low catalyst loading of **2** (turnover number: 6100000) highlighted the potential application of the catalytic system. Monoalkyl and dialkyl zinc reagents displayed different reactivities and selectivities in reactions with aryl iodides catalyzed by complexes **2** or **3**, and isomerization in reactions involving acyclic secondary alkyl zinc derivatives was suppressed by using appropriate amounts of dialkyl zinc reagents. Based on preliminary kinetic profiles and reaction evidence, three possible pathways are proposed for the reactions involving acyclic secondary alkyl zinc reagents to rationalize the difference between monoalkyl and dialkyl zinc derivatives.

Keywords: C–C coupling · cross-coupling · palladium · tridentate ligands · zinc

Introduction

Negishi coupling, as an efficient carbon–carbon bond-formation method, has been well developed for application with alkynyl, aryl, and alkenyl zinc species as coupling partners, and the reactions are performed with phosphines as ligands in most cases.[1–3] Recently, employing primary alkyl species as viable coupling partners has been realized as well.[4–28] However, reactions involving secondary alkyl reagents bearing β-hydrogen atoms still pose a significant challenge due to competition between fast β-hydride elimination and the desired reductive elimination process.[20,29] Scheme 1 provides a simple illustration of how formation of coupling product **IV** (Path A) is rivaled by undesired reaction channel **III** to **V** (Path B).[4]

Careful optimization of catalyst system is necessary to facilitate reductive elimination over β-hydride elimination to afford the desired cross-coupled product in good yields. To date, a few successful examples are available. Hayashi et al. reported that [$PdCl_2$(dppf)]-catalyzed reaction of bromobenzene with *s*-butylzinc chloride resulted in *s*-butylbenzene in 100% yield (dppf = 1,1′-bis(diphenylphosphino)ferrocene),

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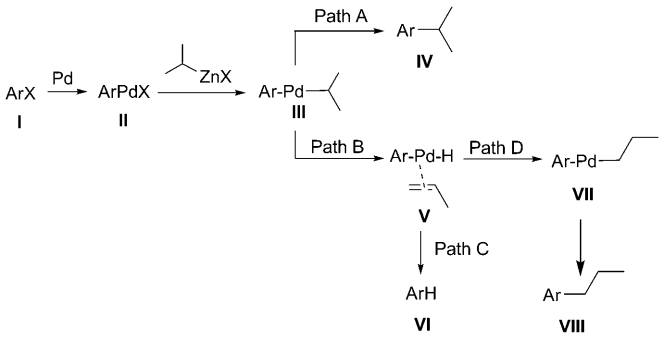


Scheme 1. Competition of β-hydride elimination with reductive elimination in Negishi coupling involving secondary alkyl zinc reagents.

and proposed that the large bite angle of dppf was responsible for the good selectivity by facilitating the reductive elimination step.[4] Fu et al. realized Negishi coupling of aryl chlorides with *s*-butylzinc chloride with $[Pd(PtBu_3)_2]$ as catalyst, and obtained the desired *s*-butyl arene compounds in good yields together with minor amounts of isomerized *n*-butyl arenes.[14] Doucet, Santelli et al. investigated the coupling of various aryl bromides with *s*-butylzinc chloride using a tetraphosphine ligand (Tedicyp), and found that selectivities are influenced by both the aryl bromides and the substrate/catalyst ratio.[20] They also examined $[\{Pd(C_3H_5)Cl\}_2]$/dppf-catalyzed coupling of diethyl zinc with aryl bromides other than bromobenzene, and the low to moderate yields were indicative of the limitations in substrate scope of the Pd/dppf system.[20] Considering the widespread existence of $C(sp^3)$–$C(sp^2)$ bonds in natural products, medicinal compounds, and materials, further exploration of the Negishi coupling of alkyl zinc reagents, especially secondary alkyl zinc reagents bearing β-hydrogen atoms,[29] to achieve highly productive coupling is of great importance. As illustrated above, developing a new generation of catalyst systems that can promote reductive elimination is generally believed to be a viable pathway.

A Pd^{II}/Pd^{IV} catalytic cycle might provide a solution to the aforementioned challenge, since Canty, van Koten et al. suggested that reductive elimination of $R^1Pd^{IV}R^2$ is a fast process.[30,31] Such a cycle is still under debate.[31–39] Increasing the electron density on the Pd^{II} center by adjusting the surrounding ligands could in principle facilitate its oxidation to Pd^{IV}, which is possibly the most difficult step compared to subsequent transmetalation or reductive elimination, because transmetalation delivering an electron-donating R group to the Pd^{IV} center should be a facile process, and reductive elimination of R^1-Pd^{IV}-R^2 has been suggested to be a fast process by stoichiometric studies.[30,31]

It is well known that the proximal thiolate ligands in biologically significant metalloenzymatic oxygenase systems such as P450 and chloroperoxidase play a significant role in the formation of high-valent Fe^{IV} heme cation radicals through electron donation, denoted the "push" effect.[40–44] This led us to postulate that sulfur-containing ligands may be good candidates to stabilize the Pd^{IV} center during catalysis. In the family of sulfur-containing ligands, thiourea and thioamide motifs have been established to be electronically modular, synthetically accessible, and efficient in inter alia Heck and Suzuki reactions under aerobic conditions by us and others.[45–57] By conjugation, the electron density of the nitrogen atom in the backbone of the ligand could be transferred to the sulfur atom to help stabilize the electron-deficient Pd^{IV} intermediate (Figure 1a). The other, neutral resonance form is known to be effective in stabilizing the Pd^{II} species.[45,47,48,54,56,57] These considerations prompted us to design and synthesize SNS thioamide pincer ligand **1**, of which the two H atoms attached to the N atoms in the backbone were expected to be deprotonated to afford a highly electron donating thioimide ligand (Figure 1b), and the tridentate nature of the ligands would make ligand dissociation difficult, and thus could possibly prevent reduction of the Pd^{II} center to Pd^0 species.[58] Herein we document our recent achievement of palladium-catalyzed, selective, and efficient Negishi coupling involving both primary and secondary alkyl zinc reagents by employing **1** as ligand and corresponding mechanistic discussions.

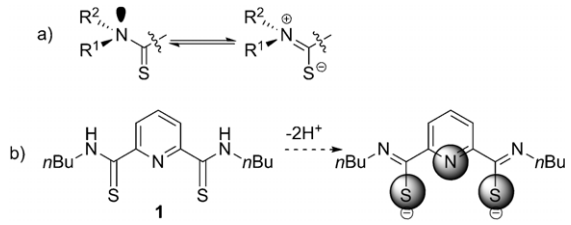


Figure 1. a) Electronic resonance of thiourea- and thioamide-type ligands. b) Speculated deprotonation process of ligand **1**.

Results and Discussion

Syntheses of the pincer ligand and corresponding palladium complexes

*Syntheses of pincer ligand **1** and its Pd complex **2***: Pincer thioamide ligand **1** was prepared from the corresponding pincer amide. In pincer amide palladium complexes, ligands usually coordinate to the palladium center through the two nitrogen anions on the amide backbone and one neutral nitrogen atom on the pyridine ring.[59–62] Reaction of **1** with $[PdCl_2(MeCN)_2]$ cleanly produced complex **2** in 95% yield [Eq. (1)]. The structure of **2** was confirmed by X-ray analysis (Figure 2a). Each ligand coordinates to one palladium atom through two sulfur and one nitrogen atoms as electron donors, and the two H atoms attached to the N atoms in the backbone of the ligand were preserved.

*Reaction of complex **2** with cyclohexylzinc chloride*: Generally, when treated with alkyl zinc reagents, Pd^{II} species can easily be reduced to Pd^0 through transmetalation followed

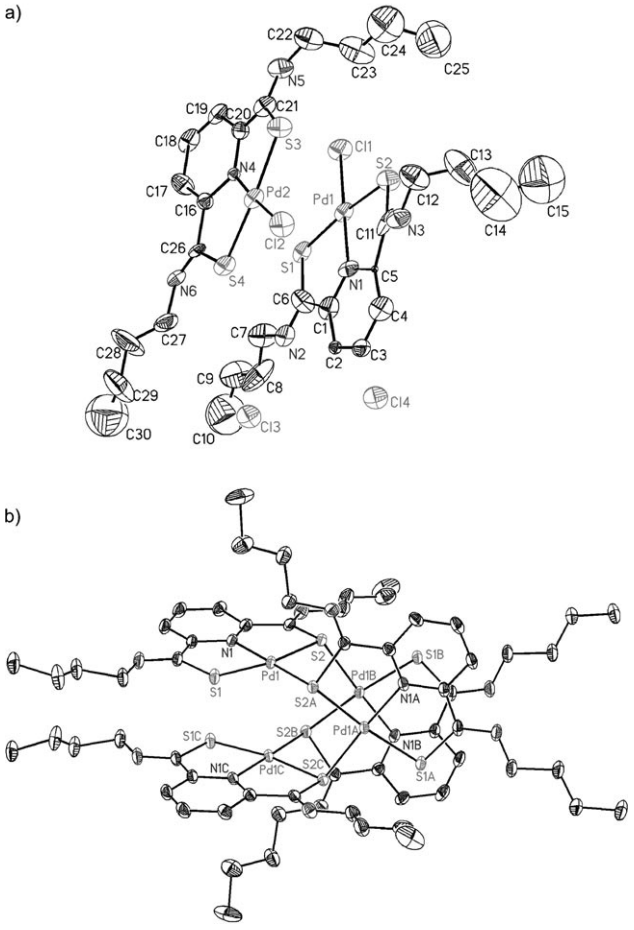
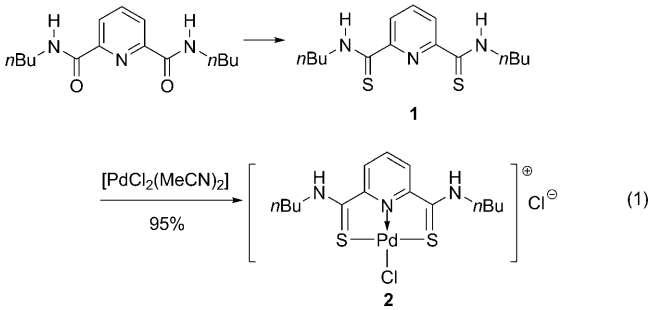
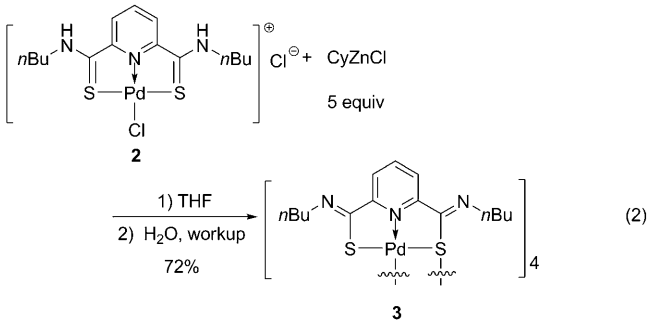


Figure 2. a) Crystal structure of **2.** b) Crystal structure of **3**.

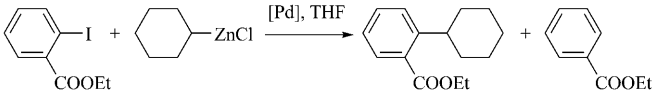


by β-hydride elimination or reductive elimination. However, when **2** was treated with an excess of cyclohexylzinc chloride, no palladium black was observed. Instead, the two hydrogen atoms attached to the nitrogen atoms were deprotonated as expected, and novel pincer thioimide Pd^{II} complex **3** was isolated [Eq. (2)]. In complex **3**, two anionic sulfur atoms as strong electron donors together with one neutral sulfur and one neutral nitrogen atom provide the palladium center with an adjustable, electron-rich, and stable coordination environment. The structure of complex **3** was confirmed by X-ray analysis (Figure 2b). These results indicated that the electron-donating properties and the tridentate nature of the ligands stabilized the Pd^{II} center in the presence of reductive organozinc reagents, as expected, and both complexes **2** and **3** could hardly be reduced to Pd^0 by cyclohexylzinc chloride under the reaction conditions.



Optimization of reaction conditions: Negishi coupling of ethyl 2-iodobenzoate with cyclohexylzinc chloride: To address coupling reactions involving secondary alkyl groups, we chose the reaction between ethyl *o*-iodobenzoate (**4a**) and cyclohexylzinc chloride (**5a**) as model to investigate the catalytic efficiency of complexes **2** and **3**. As shown in Table 1, the reaction occurred readily at 60 °C with 0.1–2 mol % of **2**, and yields and selectivities ranged from good to excellent (Table 1, entries 1–3). Remarkably, the reaction proceeded smoothly with 0.1 mol % of **2** at room temperature to furnish 96 % of **6a** with 100 % conversion of **4a** over 20 min (Table 1, entry 6). Similar yield and selectivity were obtained when 0.1 mol % of **3** was employed as catalyst at room temperature (Table 1, entry 7). In contrast, catalysis

Table 1. Optimization of reaction conditions and comparison of catalyst activity.[a]



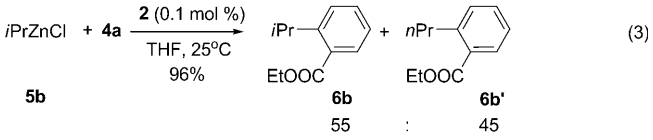
Entry	[Pd] (mol %)	Conversion [%]	Selectivity (**6a**/**7a**)	Yield of **6a** [%]
1[b]	**2** (2)	100	90/10	90
2[b]	**2** (0.5)	100	92/8	92
3[b]	**2** (0.1)	100	92/8	92
4[b,c]	**2** (0.001)	100	91/9	91
5[b,d,e]	**2** (0.00001)	71	87/13	61
6[c]	**2** (0.1)	100	96/4	96
7[c,f]	**3** (0.1)	100	98/2	98
8[c]	$[PdCl_2(dppf)]$ (0.1)	9	–	9

[a] Reaction conditions: **4a** (1.0 mmol), **5a** (2.0 mmol), THF (3.0 mL), 25 °C, 20 min. Conversions and yields were determined by GC with naphthalene as internal standard. [b] The reaction was performed at 60 °C. [c] **4a** (3.0 mmol), **5a** (6.0 mmol), THF (9.0 mL). [d] **4a** (70 mmol), **5a** (100 mmol), THF (150 mL). [e] Detected at 96 h. [f] Detected at 40 min.

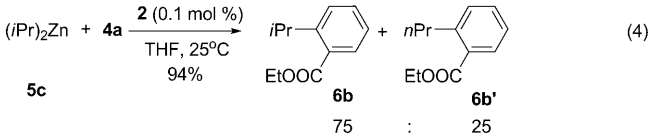
with [$PdCl_2$(dppf)] under otherwise identical conditions suffered from low reactivity (Table 1, entry 8).

The catalytic capability of **2** was further explored by lowering the catalyst loading to 0.001 mol% at 60°C, and 91% of **6a** was formed after 6 h (Table 1, entry 4). To probe the practicality, 19.35 g (70 mmol) of **4a** was allowed to couple with **5a** (100 mmol) in the presence of 7.0×10^{-6} mmol of **2** at 60°C. After 96 h, 61% of **6a** was detected by GC (Table 1, entry 5), that is, the turnover number (TON) for this reaction was 6.1×10^{6}, and the turnover frequency 6.4×10^{4} h^{-1}.

Negishi coupling of aryl iodides with secondary alkyl zinc reagents: Negishi coupling of secondary alkyl zinc reagents often suffers from dehalogenation (Scheme 1, path C) or isomerization problems (Scheme 1, path D) brought about by β-hydride elimination. Though a trace of dehalogenated product was observed in the model reaction catalyzed by **2** (vide supra), the reaction of **4a** with isopropylzinc chloride (**5b**) catalyzed by 0.1 mol% of **2** afforded a 96% yield of cross-coupled products as a mixture of 55% of branched product **6b** (unisomerized) and 45% of linear product **6b′** (isomerized) [Eq. (3)]. However, the branched-to-linear ratio was improved to 75:25 when diisopropylzinc **5c** (0.55 equiv relative to **4a**) was employed as nucleophile [Eq. (4)]. Moreover, the reaction of **5c** with **4a** was exothermic in the beginning, while no obvious exothermic process was detected in the reaction of **5b** with **4a**.



(3)



(4)

In situ monitoring of the reaction of **4a** with **5c** (0.55 equiv relative to **4a**) catalyzed by 0.1 mol% of **2** at 0°C revealed that the kinetic plot was composed of a fast period and a slow period with a clear turning point when the conversion of **4a** reached around 55% (Figure 3). Consumption of the 55% of **4a** in the initial period took 9.2 min (the "fast period"), while that of the other 45% of **4a** took more than 140 min (the "slow period").

Notably, measurement of the distribution of the products by GC revealed that the branched-to-linear ratio kept changing during the reaction process (Figure 4a). In the initial few minutes, the branched product dominated, and only a trace of linear product was detected. Afterwards, the rate of formation of the former decreased while that of the latter

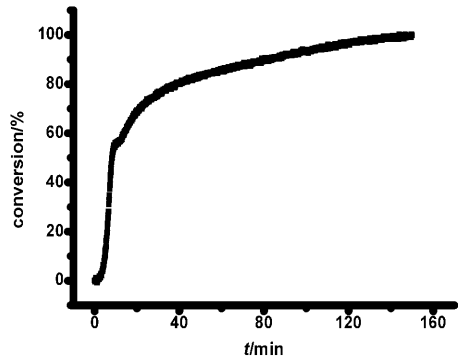


Figure 3. Kinetic plot of the reaction of **4a** and **5c** at 0°C with [**4a**] = 1.00 M, [**5c**] = 0.55 M, and [**2**] = 0.0017 M.

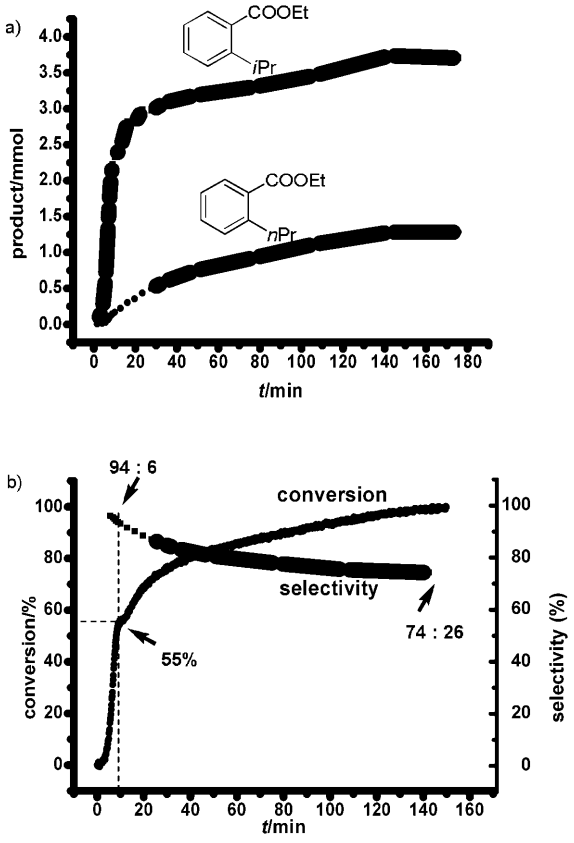
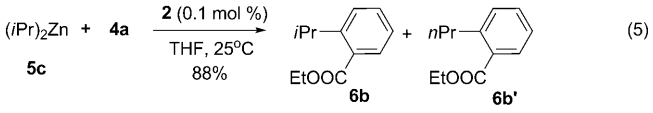


Figure 4. a) Product distribution plots of the reaction of **4a** and **5c** at 0°C with [**4a**] = 1.00 M, [**5c**] = 0.55 M, and [**2**] = 0.0017 M. b) Conversion of **4a** versus time and selectivity (branched-to-linear ratio) versus time of the same reaction.

increased. As shown in Figure 4b, the branched-to-linear ratio was 94:6 when the conversion of **4a** reached 55%, and decreased with time to 74:26 at the end, consistent with Equation (4). Statistically, the first 55% of **4a** reacted with diisopropylzinc (**5c**) and resulted in the cross-coupled product and 55% of isopropylzinc iodide, and subsequently the remaining 45% of **4a** reacted with the isopropylzinc iodide formed in situ. Therefore, we envisioned that the reaction of **4a** with **5c** accounted for the fast period and high selectivity,

and the reaction of **4a** with isopropylzinc iodide for the slow period and low selectivity. Consequently, good selectivity could possibly be obtained by treating **4a** with more than 1 equiv of **5c**.

Indeed, the branched-to-linear ratio of the products improved to 98:2 when 1.5 equivalents of **5c** reacted with **4a** at 0 °C [Eq. (5)]. The kinetic plot of the reaction corresponded to a single "fast process" as expected, and over 70% of **4a** was consumed over 2 min (Figure 5a).



(5)

Inspired by the above results, we further examined the coupling of aryl halides with secondary alkyl zinc nucleophiles catalyzed by complex **2** (Table 2). The reactions of aryl iodides bearing ester, amide, and even carboxyl groups with cyclohexylzinc chloride (**5a**) proceeded smoothly (Table 2, entries 1, 2, 4, and 5). Ethyl *o*-bromobenzoate (**4d**) coupled with **5a** in good yield as well (Table 2, entry 3). Isomerization occurred when isopropylzinc chloride (**5b**) reacted with **4e** (Table 2, entry 6), yet the branched-to-linear ratio was higher than that of the reaction of **5b** with **4a** [Eq. (3)]. Utilizing diisopropylzinc (**5c**) instead improved the selectivity to 95:5, as expected (Table 2, entry 7). High selectivities were similarly attained in other reactions of secondary dialkyl zinc reagents with aryl iodides (Table 2, entries 9–13). Similar yields and selectivities were obtained when 0.1 mol% of **3** was used as catalyst (Table 2, entries 1, 2, 9–11).

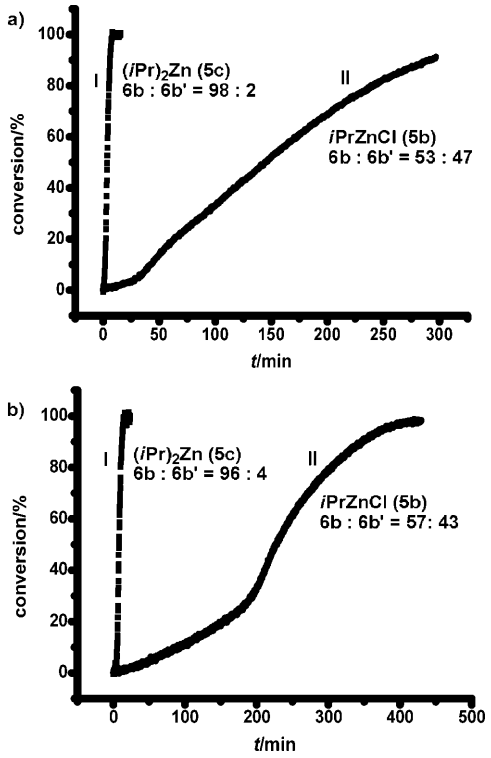
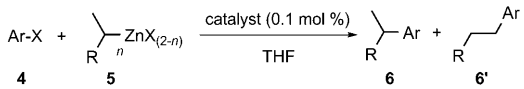
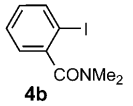
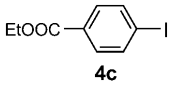
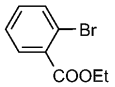
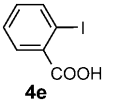
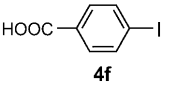
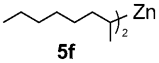


Figure 5. a) Kinetic profiles of reactions catalyzed by **2**. Curve I: kinetic plot of the reaction of **4a** and **5c** at 0 °C with [**4a**] = 0.33 M, [**5c**] = 0.50 M, [**2**] = 0.0017 M; Curve II: kinetic plot of the reaction of **4a** and **5b** at 0 °C with [**4a**] = 0.33 M, [**5b**] = 0.50 M, [**2**] = 0.0017 M. b) Kinetic profiles of reactions catalyzed by **3**. Curve I: kinetic plot of the reaction of **4a** and **5c** at 0 °C with [**4a**] = 0.33 M, [**5c**] = 0.50 M, [**3**] = 0.0017 M; Curve II: kinetic plot of the reaction of **4a** and **5b** at 0 °C with [**4a**] = 0.33 M, [**5b**] = 0.50 M, [**3**] = 0.0017 M.

Table 2. Negishi coupling of secondary alkyl zinc reagents catalyzed by **2** or **3**.[a]

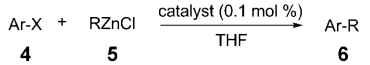


Entry	4	5[b]	Product	Yield [%][c] (6+6′)	Selectivity[d] (6:6′)
1	 4b	**5a**	**6c**	97 (82)	–
2	 4c	**5a**	**6d**	80 (81)	–
3	 4d	**5a**	**6a**	85	–
4[e]	 4e	**5a**	**6e**	94	–
5[e]	 4f	**5a**	**6f**	83	–
6[e]	**4e**	**5b**	**6g**	90	86:14
7[e]	**4e**	**5c**	**6g**	87	95:5
8	**4a**	*s*BuZnCl **5d**	**6h**	88	56:44
9	**4b**	**5c**	**6i**	72 (74)	95:5 (95:5)
10	**4a**	*s*Bu$_2$Zn **5e**	**6h**	84 (89)	92:8 (93:7)
11	**4b**	**5e**	**6j**	77 (77)	97:3 (95:5)
12	**4a**	 5f	**6k**	85	93:7
13	**4b**	**5f**	**6l**	88	97:3

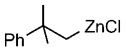
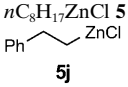
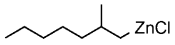
[a] Reaction conditions: **4** (3 mmol), **2** (0.1 mol%), RZnX (6 mmol), THF (9 mL) or R_2Zn (6 mmol), THF (12 mL), 25 °C. [b] R_2Zn or RZnX were prepared in situ from RMgX and $ZnCl_2$. [c] Yield of isolated product. The data in parentheses are the yields of isolated products for the reactions catalyzed by **3** (0.1 mol%). [d] Detected by GC. The data in parentheses are the selectivities of the reactions catalyzed by **3** (0.1 mol%). [e] **4** (1 mmol), R_2Zn (3 mmol) or RZnX (3 mmol), **2** (0.5 mol%), THF (6 mL), 40 °C; the yield and selectivity were determined by ^{1}H NMR spectroscopy.

Negishi coupling of aryl iodides with primary alkyl zinc compounds: We next investigated the coupling of aryl iodides with primary alkyl zinc nucleophiles catalyzed by both complexes **2** and **3** (Table 3). The reactions catalyzed by either catalyst displayed good generality towards primary alkyl zinc chlorides. At room temperature, (2-methyl-2-phenylpropyl)zinc chloride **5g** did not react with **4a**, probably

Table 3. The Negishi-coupling of primary alkyl zinc reagents with aryl iodides catalyzed by **2** or **3**.



4 **5** **6**

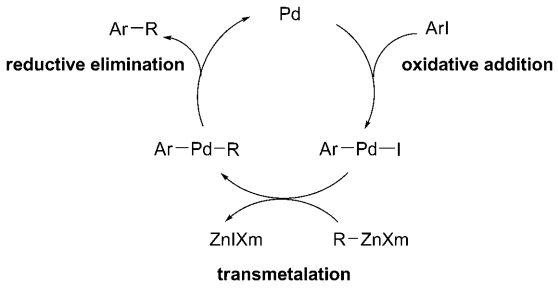
Entry	ArX	RZnCl[b]	Product	Yield of **6**[c] [%]
1	**4a**	 **5g**	**6m**	0
2	**4a**	**5g**	**6m**	97 (99)[d]
3	**4a**	*n*BuZnCl **5h**	**6n**	84 (78)
4	**4a**	$nC_8H_{17}ZnCl$ **5i**	**6o**	81 (77)
5	**4a**	 **5j**	**6p**	98 (87)
6	**4a**	 **5k**	**6q**	90 (81)
7	**4a**	$nC_{12}H_{15}ZnCl$ **5l**	**6r**	77 (79)
8	**4b**	**5h**	**6s**	91 (78)
9	**4b**	**5j**	**6t**	98 (99)
10	**4c**	**5j**	**6u**	77 (91)
11	**4e**	**5h**	**6v**	94[e]
12	**4f**	**5h**	**6w**	76[e]

[a] Reaction conditions: **4** (3 mmol), **5** (6 mmol), **2** (0.1 mol%), THF (9 mL), 25°C . [b] RZnCl **5** were prepared in situ from RMgX and $ZnCl_2$. [c] Yield of isolated product. The data in parentheses are the yields of isolated products for the reactions catalyzed by **3** (0.1 mol%). [d] The reaction was performed at 60°C. [e] **4** (1 mmol), RZnX (3 mmol), **2** (0.5 mol%), THF (6 mL), 40°C; the yield and selectivity were determined by ^1H NMR spectroscopy.

due to steric hindrance around the reaction site, but when the reaction temperature was raised to 60°C, 97% of product **6m** was obtained (Table 3, entries 1 and 2). Other primary alkyl zinc reagents such as **5h–5l** bearing β-hydrogen or one *ortho*-methyl group adjacent to the reaction site reacted smoothly with **4a** at 25°C and afforded the corresponding cross-coupled products **6n–6r** in good to excellent yields (Table 3, entries 3–7). The reactions of *o*-iodo-*N*,*N*-dimethylbenzamide (**4b**) with *n*-butylzinc chloride (**5h**) or phenethylzinc chloride (**5j**) and of ethyl *p*-iodobenzoate **4c** with **5j** all afforded good results (Table 3, entries 8–10).[63] Coupling reactions involving **4e** and **4f** bearing a carboxyl group required higher temperatures, but the yields ranged from good to excellent and the functional groups were well preserved (Table 3, entries 11 and 12).

Preliminary mechanistic discussion on Negishi coupling promoted by 2 or 3: Dialkyl zinc compounds exhibited much higher reactivities and selectivities than mono-alkyl zinc reagents in Negishi coupling with aryl iodides catalyzed by **2** or **3** (vide supra). To gain insight into this difference, we monitored the kinetics of the reactions of **4a** with *i*PrZnCl (**5b**) and of **4a** with iPr_2Zn (**5c**) at 0°C. As shown in the reaction of **4a** with **5b** catalyzed by 0.5 mol% of **2** at 0°C showed an induction period of 30 min, and needed around 5 h for completion (Figure 5a, curve II). The branched-to-linear ratio of the products was 53:47. On the other hand, the reaction of **4a** with **5c** was completed within 8 min (Figure 5a, curve I), and the selectivity was 98:2. Similar differences between the two alkyl zinc reagents were found in the reactions catalyzed by **3** at 0°C (Figure 5b).

It is generally accepted that Pd-catalyzed Negishi coupling proceeds through oxidative addition, transmetalation, and reductive elimination successively in a catalytic cycle (Scheme 2). If both reactions above followed this simplified

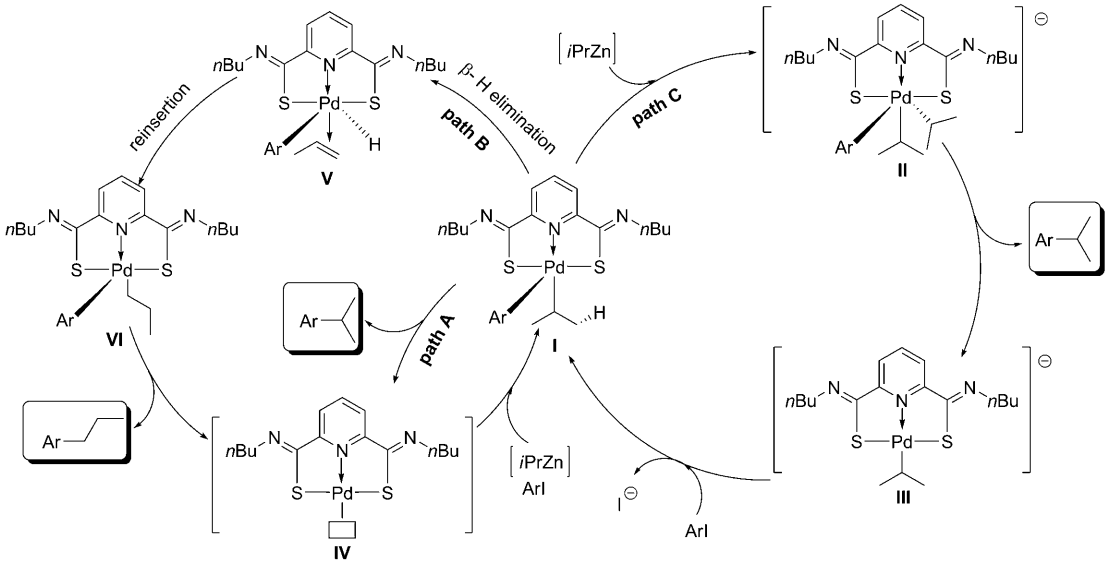


Scheme 2. General mechanistic pathway of Pd-catalyzed Negishi coupling.

catalytic cycle, the difference between them would lie only in the transmetalation step. In this case, if transmetalation were the rate-determining step, the two reactions would exhibit different reaction rates and similar selectivities; if transmetalation were not rate-determining, the two reactions would show similar reactivities and selectivities. Therefore, the different reactivities and selectivities observed above indicate that the two reactions follow different mechanistic pathways.

Reactions catalyzed by pincer ligand Pd complexes are usually performed at high temperature, which is proposed to be a prerequisite for the catalyst precursors to break down to colloidal metallic palladium and start a Pd^0/Pd^{II} catalytic cycle.[37,64] However, in our system, the reactions proceeded readily at room temperature or even at 0°C. Moreover, thioimide pincer Pd^{II} complex **3** was isolated from the reaction of pincer thioamide Pd complex **2** with an excess of cyclohexylzinc chloride (**5a**), that is, both **2** and **3** are hard to reduce to Pd^0 species by organozinc reagents under the reaction conditions. Therefore, we speculated that the catalytic cycles of the reactions catalyzed by **2** or **3** were initiated by a Pd^{II} species.

Considering the different reactivities and selectivities of monoalkyl zinc chloride and dialkyl zinc reagents as nucleophiles and the stabilizing capability of the ligand towards the Pd center, we proposed a high-valent Pd species **I**, generated from the reaction of a Pd^{II} species with aryl iodides, as a common intermediate. Three possible competitive pathways from the intermediate are illustrated in Scheme 3. Species **I** may directly undergo reductive elimination and afford the branched product (path A), or proceed through β-hydride elimination followed by re-insertion and reductive elimination to form the linear product (path B). Also, **I** could be further alkylated by organozinc reagents to produce anionic hexacoordinate Pd^{IV} species **II**, which could

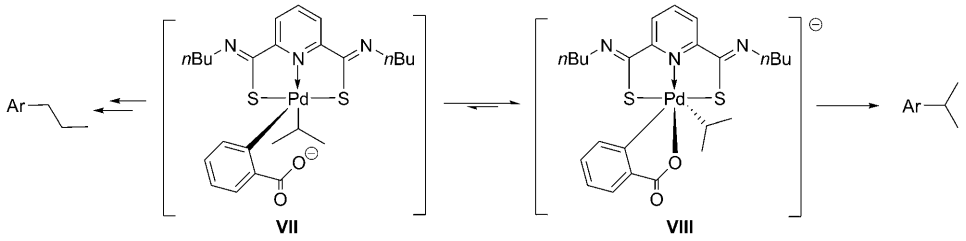


Scheme 3. Speculated competitive pathways for Negishi coupling of aryl iodides with **5b** or **5c** catalyzed by **2** or **3**.

furnish the branched product by reductive elimination (path C).

The differences between the reactions of **4a** with **5b** and **4a** with **5c** could be rationalized by the proposed pathways. Highly nucleophilic and reactive **5c** might further alkylate **I** to form **II**, in which no vacant site is available for β-hydride elimination and consequently for isomerisation to occur. Hence, path C is possibly the major way in the reaction of **5c** with aryl iodides. On the other hand, further alkylation of **I** by less reactive **5b** is probably hard to achieve, so **I** should undergo direct reductive elimination to afford the branched product (path A), and competitively undergo β-hydride elimination to afford the linear product (path B) when **5b** is the nucleophile.

Currently, we have not gained any direct evidence regarding Pd^{IV} species **I** and **II** proposed in Scheme 3. The Pd^{II}/Pd^{IV} catalytic cycles were mainly based upon the fact that complex **3** is stable in the presence of the alkyl zinc reagents, and the high efficiency of the reactions catalyzed by either complex **2** or **3** under mild conditions, which made the dissociation of the highly electron donating tridentate ligand less probable. In addition to the differences between isopropylzinc chloride (**5b**) and diisopropylzinc (**5c**) in the reaction system, another piece of evidence supports the feasibility of the above hypothetic catalytic cycles. The selectivity of the reaction of ethyl 2-iodobenzoate (**4a**) with **5b** was 55:45 [Eq. (3)], while that of 2-iodobenzoic acid (**4e**) with **5b** was 84:16 (Table 2, entry 6). The difference could be rationalized by the existence of complex **VII** resulting from the reaction of intermediate **IV** with **4e** and **5b** following a similar route to that in Scheme 3. The carboxylate anion of complex **VII** would favorably bind to the Pd center in an intramolecular manner to form hexacoordinate complex **VIII**, which would prefer direct reductive elimination over β-hydride elimination and consequently result in improved selectivity (Scheme 4).



Scheme 4. Proposed pathway for the reaction of **4e** with **5b**.

Conclusion

In summary, a pincer thioamide Pd complex and a pincer thioimide Pd complex were documented to stay as Pd^{II} species in the presence of alkyl zinc reagents. The catalytic capabilities of the two sulfur-containing palladium species were explored in Negishi reactions involving primary and secondary alkyl zinc reagents. These reactions readily occurred under mild conditions, tolerated substrates with β-hydrogen atoms, and performed catalysis with unusually high efficiency. The operational simplicity of these processes, in conjunction with the easy accessibility of both catalysts and substrates, promises synthetic utility of this new methodology. An experiment on a scale of 19.35 g carried out at very low catalyst loading highlighted its potential applications.

Mechanistic pathways were proposed on the basis of preliminary results. Further detailed mechanistic studies are underway in and will be reported in due course.

Experimental Section

All manipulations were carried out under an inert atmosphere by using an argon-filled glove box or standard Schlenk techniques. All glassware was oven-dried at 120 °C for more than 1 h prior to use. Dichloromethane was dried and distilled from calcium hydride. Tetrahydrofuran was dried and distilled from sodium/benzophenone immediately prior to use under nitrogen atmosphere. CH_3CN was distilled from P_2O_5 and degassed by purging with nitrogen for more than 45 min. DMF was obtained from commercial sources and dried with molecular sieves (4 Å). ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz NMR spectrometer. High-resolution mass spectra (HRMS) were measured with a Waters Micromass GCT instrument and accurate masses are reported for the molecular ion $[M^+]$. GC yields were recorded with a Varian GC 3900 gas chromatography instrument with an FID detector. For the ReactIR kinetic experiments, the reaction spectra were recorded on an IC 10 from Mettler-Toledo AutoChem fitted with a diamond-tipped probe. Data manipulation was carried out with the iC IR software, version 1.05. Crystal diffraction intensity data were collected on a Bruker CCD 4K diffractometer with graphite-monochromatized $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Lattice determination and data collection were carried out with SMART version 5.625 software. Data reduction and absorption corrections were performed with SAINT version 6.45 and SADABS version 2.03. Structure solution and refinement were performed with the SHELXTL version 6.14 software package.

Synthesis of pincer ligand 1: A mixture of N^2,N^6-dibutylpyridine-2,6-dicarboxamide[65] (15.27 g, 55 mmol) and Lawesson's reagent (22.25 g, 55 mmol) was heated at 100 °C in toluene for 4 h. The insoluble product was filtered while hot. The solution was evaporated to dryness and purified by column chromatography (neutral alumina, 20% ethyl acetate in petroleum ether). The product **1** was isolated as a yellow microcrystalline solid (yield: 14.73 g; 87%). ^1H NMR (300 MHz, 25 °C, [D$_6$]DMSO): $\delta =$ 0.91 (t, $J = 7.2$ Hz, 6H), 1.43–1.31 (m, 4H), 1.75–1.65 (m, 4H), 3.88–3.81 (m, 4H), 8.09 (t, $J = 7.8$ Hz, 1H), 8.66 (d, $J = 7.8$ Hz, 2H), 11.05 ppm (br, 2H); ^{13}C NMR (75.4 MHz, 25 °C, [D$_6$]DMSO): $\delta = 13.87$, 19.98, 29.47, 45.24, 127.00, 138.54, 149.73, 189.51 ppm; HRMS: m/z calcd for $C_{15}H_{23}N_3S_2$ $[M]^+$: 309.1333; found: 309.1343.

Synthesis of Pd complex 2: A solution of ligand **1** (3.09 g, 10 mmol) in CH_3CN (30 mL) was added to a refluxing solution of $[PdCl_2(MeCN)_2]$ (2.59 g, 10 mmol) in CH_3CN (100 mL) under N_2. An orange solid precipitated immediately. The reaction mixture was stirred for 3 h under reflux. Then mixture was cooled to room temperature, filtered, and the residue washed with diethyl ether and dried for 2 h under vacuum to afford Pd complex **2** (yield: 4.67 g, 93%). ^1H NMR (300 MHz, 25 °C, [D$_6$]DMSO): $\delta = 0.95$ (t, $J = 7.2$ Hz, 6H), 1.50–1.37 (m, 4H), 1.83–1.73 (m, 4H), 3.78 (t, $J = 6.9$ Hz, 4H), 8.56 (t, $J = 7.8$ Hz, 1H), 8.80–8.78 ppm (m, 2H); ^{13}C NMR (75.4 MHz, 25 °C, [D$_6$]DMSO): $\delta = 13.78$, 20.03, 29.03, 48.23, 127.45, 140.36, 156.01, 187.81 ppm; HRMS: m/z calcd for $C_{15}H_{22}N_3S_2ClPd$ $[M-Cl]^+$: 450.0057; found: 450.0064.

Synthesis of Pd complex 3: Dry THF (12 mL) and cyclohexyl zinc chloride (0.9 M in THF, 1.1 mL) were added to Pd complex **2** (225.2 mg, 0.46 mmol) under N_2 (50 mL), and the resulting red suspension was stirred at room temperature overnight, till the reaction mixture became a clear solution. Then 10 mL of water was added, and volatile substances were removed on a rotary evaporator. The remaining mixture was extracted with CH_2Cl_2 (3×15 mL), and the organic phases were combined and dried over Na_2SO_4. After filtration, the filtrate was concentrated till solid appeared. On addition of hexane (20 mL), a reddish orange solid precipitated, which was collected by filtration, washed with hexane, and dried under vacuum for 2 h to afford **3** as a reddish orange solid (yield: 180 mg, 94%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.87$ (t, $J =$ 7.4 Hz, 3H), 0.98 (t, $J = 7.4$ Hz, 3H), 1.37–1.25 (m, 2H), 1.63–1.47 (m. 4H), 1.86–1.74 (m, 2H), 3.36–3.28 (m, 2H), 3.92–3.79 (m, 2H), 7.81 (t, $J = 6.9$ Hz, 1H), 8.05 (d, $J = 7.2$ Hz, 1H), 8.12 ppm (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 13.96$, 20.82, 32.13, 32.21, 52.51, 54.80, 124.82, 125.55, 136.96, 157.35, 157.80, 160.88, 167.74 ppm; HRMS (MALDI/DHB): m/z calcd for $C_{60}H_{85}N_{12}S_8Pd_4$ $[M+H]^+$: 1653.0925; found: 1653.0920.

Ethyl 2-butylbenzoate (6n): Zinc chloride (6 mmol) was added to a Schlenk tube in glove box, which was sealed with a rubber septum and transferred out. After THF (3 mL) was injected into the tube, the reaction mixture was cooled to 0 °C and *n*-butylmagnesium bromide (6 mmol) was added dropwise. Then the mixture was stirred for 1 h at 25 °C, and Pd complex **3** (1.3 mg, 0.003 mmol) and ethyl 2-iodobenzoate (828.2 mg, 3 mmol) were added. The resultant mixture was stirred for another 2 h at 25 °C. The suspension generated was quenched with dilute hydrochloric acid (5 mL, 2 M) and extracted with ethyl acetate. The combined extracts were washed with aqueous $NaHCO_3$ solution and $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, and subjected to silica-gel chromatography to give pure **6n** was (519.8 mg, 84% yield). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.75$ (d, $J = 7.8$ Hz, 1H), 7.29 (t, $J =$ 7.5 Hz, 1H), 7.15–7.10 (m, 2H), 4.26 (q, $J = 7.2$ Hz, 2H), 2.85 (t, $J =$ 7.5 Hz, 2H), 1.54–1.44 (m, 2H), 1.34–1.27 (m, 5H), 0.84 ppm (t, $J =$ 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 13.83$, 14.11, 22.65, 33.88, 34.05, 60.57, 125.45, 129.78, 130.29, 130.70, 131.44, 144.25, 167.76 ppm; HRMS: m/z calcd for $C_{13}H_{18}O_2$ $[M]^+$: 206.1307; found: 206.1310.

Acknowledgements

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