Pd-Catalyzed Cross-Coupling Reactions of Pyridine Carboxylic Acid Chlorides with Alkylzinc Reagents

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Abstract: The efficient cross-coupling reaction to afford ketones from pyridine carboxylic acid chlorides and alkylzinc reagents in the presence of Pd(phen)Cl₂ is reported. In the case of chloronico-tinoyl chlorides, none of Negishi cross-coupling products of 2-chloroazine moiety was formed. The catalyst loading could be reduced up to 0.01 mol%.

Key words: cross-coupling, alkylzinc reagents, palladium, pyridine, ketone

The acylation reaction of organometallic reagents affords one of the most important methods for ketone synthesis and numerous studies have been reported.¹ Friedel–Crafts acylation with acid chlorides is a complementary method for the synthesis of aromatic ketones;² however, undesirable orientation and/or the usage of more than a stoichiometric amount of Lewis acids sometimes limit its application. Weinreb amide methodology³ is also a useful technique, but has a limitation to synthesize pharmaceuticals and target molecules for material science because of poor functional compatibility of Grignard reagents and organolithium compounds. Therefore, transition-metalcatalyzed or -mediated reactions of carboxylic acid derivatives with functionalized organometallic reagents⁴ provide most potent procedures.

The use of organozinc reagents has become a subject of current interest in organic synthesis because of their great tolerance for broad functional groups.⁵ Some reactions using metallic zinc and organozinc reagents with carbonyl compounds to provide olefins, alcohols, and amines have been reported in our laboratory.⁶ Transition-metal-catalyzed C–C bond formation reactions of organozinc compounds with aromatic halides are well known as Negishi cross-coupling,^{5,7} as well as acylation reaction with carboxylic acid derivatives.^{1a,5} Since Negishi et al. reported the palladium-catalyzed acylation of organozinc reagents,⁸ extensive efforts^{9–12} have been made including Fukuyama's thioester cross-coupling¹³ for various scopes and wide applications.

Interestingly, there have been few reports about formation of pyridyl ketones via the cross-coupling reactions,¹⁴ whereas traditional Friedel–Crafts acylation was unsuitable for pyridine rings because of their electron deficiency and limitation of substitution orientation. So, crosscoupling reaction of pyridine carboxylic acid chlorides with organometallic reagents would provide a superior method for them. Knochel et al. reported only one example of acylation between 6-chloronicotinoyl chloride and diarylzinc.^{14a} Wang et al. had demonstrated an addition reaction of Grignard reagents to 6-chloronicotinoyl chloride in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl]ether.^{14b} Those examples are limited to alkyl Grignard reagents and some functionalized aryl organometallics, and the scope of this method has not been fully explored. This situation encouraged us to attempt the cross-coupling reaction between functionalized alkylzinc reagents and pyridine carboxylic acid chlorides. Here, we would like to

 Table 1
 Palladium-Catalyzed Cross-Coupling of 1 with 2



Entry	Palladium catalyst	Solvent	Product	Yield (%) ^a
1	Pd(PPh ₃) ₄	toluene	3a	68
2	Pd(PPh ₃) ₄	toluene	3b	94
3	Pd ₂ (dba) ₃ CHCl ₃	toluene	3a	65
4	Pd(PPh ₃) ₄	MeCN	3a	47 ^b
5	$PdCl_2(PPh_3)_2$	MeCN	3a	58 ^b
6	_	MeCN	3a	5
7	Pd ₂ (dba) ₃ CHCl ₃	MeCN	3a	60
8	PdCl ₂	MeCN	3a	83
9	Pd(OAc) ₂	MeCN	3a	75
10	Pd(bpy)Cl ₂	MeCN	3a	86
11	Pd(phen)Cl ₂	MeCN	3a	92
12	Pd(phen)Cl ₂	MeCN	3a	91°
13	Pd(phen)Cl ₂	MeCN	3b	94

^a Isolated yield.

^b Compounds 4–6 were observed.

^c The amount of 2.5 equiv of alkylzinc reagent **2** was used. None of 2-alkylated product **4** was detected.

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report an efficient cross-coupling reaction of pyridine carboxylic acid chlorides with functionalized alkylzinc reagents.

First, we examined the reaction between 6-chloronicotinoyl chloride (1a) and alkylzinc reagent 2^{15} based on Tamaru's condition as shown in Table 1.^{12,16} In the presence of Pd(PPh₃)₄, cross-coupling reaction carried out at ambient temperature, and the corresponding ketone 3a was obtained in 68% yield (Table 1, entry 1). In the previous report,^{6d} ethyl acetate and acetonitrile were better solvents compared to toluene for nucleophilic addition of alkylzinc reagents to aromatic aldimines. So, next we chose acetonitrile as a solvent, however, only 47% of 3a was obtained with considerable amount of byproducts 4-6 (Scheme 1, Table 1, entry 4). 2-Alkylated pyridines 4 and 6 were formed from Negishi cross-coupling reaction between alkylzinc reagent 2 and 2-chloroazine moiety of 6-chloronicotinoyl chloride (1a).¹⁷ On the other hands, aldehydes 5 and 6 were obtained through the β -H elimination of a palladium alkyl intermediate followed by the reductive elimination of the palladium hydride species.^{11,18} Catalytic activity should be controlled to prevent Negishi cross-coupling reaction of 2-chloroazine moiety and β-H elimination of alkylzinc reagents from occurring and achieve selective formation.

Various catalysts and reaction conditions were examined as shown in Table 1. When PPh₃ was used as a ligand, yields were moderate and considerable amount of byproducts **4–6** were observed. The yield was remarkably low in the absence of Pd catalyst (entry 6). Interestingly, in the case of ligandless catalysts such as PdCl₂ or Pd(OAc)₂, better results were obtained in 83% and 75% yields, respectively (entries 8 and 9). This might show the possibility that 1a or 3a themselves worked as a ligand, so palladium catalysts having bidentate nitrogen ligands, such as 2,2'-bipyridine (bpy) and 1,10-phenanthroline (phen), were attempted. Among all of conditions, $Pd(phen)Cl_2$ proved to be the best catalyst and excellent yield was achieved (entry 11). Under this optimized reaction conditions [1.5 equiv of alkylzinc reagents and 3 mol% of Pd(phen)Cl₂],¹⁹ none of the byproducts 4-6 was observed, even if the excess amount (2.5 equiv) of alkylzinc reagent 2 was used (entry 12).²⁰ Pd(phen)Cl₂ catalyst system was also effective to benzoyl chloride (entry 13). The catalyst loading could be reduced up to 0.01 mol% with prolonged reaction time (Scheme 2).

To study the scope and limitations of this transformation, various acid chlorides and alkylzinc reagents were exam-



Scheme 2

 Table 2
 Pd-Catalyzed Cross-Coupling of Nicotinoyl Chlorides with Alkylzinc Reagents



^a Isolated yield.

ined, and the results were summarized in Table 2. Alkylzinc reagents bearing ester and cyano groups could be smoothly converted into corresponding ketones in high yields (entries 3–6). Chloronicotinoyl chlorides 7 and 8 also reacted successfully to afford the corresponding products 9 and 10 without any aldehydes and 2-alkylated



Scheme 1 Synlett 2009, No. 7, 1091–1094 © Thieme Stuttgart · New York Negishi cross-coupling products, respectively. Thus, the present $Pd(phen)Cl_2$ catalyst system achieved chemoselective ketone formation between chloronicotinoyl chlorides and alkylzinc reagents.

Furthermore, unsubstituted pyridine carboxylic acid chlorides were also examined (Scheme 3). These acid chlorides were commercially available as hydrochloric acid salts **11a–c**, so one equivalent excess of alkylzinc reagents were needed in these cases. The reaction between nicotinoyl chloride hydrochloride (**11a**) and alkylzinc reagent **2** gave corresponding ketone **12a** in high yield, however, picolinoyl chloride hydrochloride (**11b**) and isonicotinoyl chloride hydrochloride (**11c**) afforded moderate yields.





In the case of dicarboxylic acid dichlorides **13** and **15**, corresponding ketones **14a** and **16a** were obtained in good yields with small amount of isomerized products **14b** and **16b**, respectively (Scheme 4, Scheme 5). These isomerized ketones **14b** and **16b** were presumably formed through β -H elimination of alkylzinc reagent **2** followed by alkene reinsertion preceding reductive elimination.²¹



Scheme 4



Scheme 5

In conclusion, we have developed an efficient and chemoselective cross-coupling reaction of chloronico-

tinoyl chlorides with alkylzinc reagents in the presence of $Pd(phen)Cl_2$ to afford pyridyl ketones with no formation of Negishi coupling product of 2-chloroazine moiety. This catalyst system can be adapted to cross-coupling of various pyridine carboxylic acid chlorides with alkylzinc reagents. Further explorations for applications of this system are now in progress.

References and Notes

- (1) (a) Dieter, R. K. *Tetrahedron* 1999, 55, 4177.
 (b) Lawrence, N. J. J. Chem. Soc., Perkin Trans. 1 1988, 1739.
- (2) Heaney, H. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 733.
- (3) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* 1982, 22, 3815. (b) Balasubramaniam, S.; Aiden, I. S. *Synthesis* 2008, 3703.
- (4) Handbook of Functionalized Organometallics; Knochel, P., Ed.; Wiley-VCH: New York, 2005.
- (5) (a) Knochel, P.; Singer, R. D. Chem. Rev. 1993, 93, 2117.
 (b) Erdik, E. Organozinc Reagents in Organic Synthesis; CRC Press: Boca Raton FL, 1996. (c) Organozinc Reagents: A Practical Approach; Knochel, P.; Jones, P., Eds.; Oxford University Press: New York, 1999.
 (d) Knochel, P.; Millot, N.; Rodriguez, A.; Tucker, C. E. Org. React. 2001, 58, 417. (e) Knochel, P.; Calaza, M. I.; Hupe, E. In Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: New York, 2004.
- (6) (a) Ishino, Y.; Mihara, M.; Kageyama, M.; Nishiguchi, I. Bull Chem. Soc. Jpn. 1998, 71, 2669. (b) Ishino, Y.; Mihara, M.; Kageyama, M. Tetrahedron Lett. 2002, 43, 6601. (c) Ito, T.; Ishino, Y.; Mizuno, T.; Ishikawa, A.; Kobayashi, J. Synlett 2002, 2116. (d) Iwai, T.; Ito, T.; Mizuno, T.; Ishino, Y. Tetrahedron Lett. 2004, 45, 1083.
- (7) (a) Negishi, E.; King, A. O.; Okukado, N. J. Org. Chem. 1977, 42, 1821. (b) King, A. O.; Okukado, N.; Negishi, E. J. Chem. Soc., Chem. Commun. 1977, 683. (c) Negishi, E. Acc. Chem. Res. 1982, 15, 340.
- (8) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.
- (9) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. J. Org. Chem. 1988, 53, 2392. (b) Reddy, C. K.; Knochel, P. Angew. Chem., Int. Ed. Engl. 1996, 35, 1700.
- (10) (a) Sato, T.; Naruse, K.; Enokiya, M.; Fujisawa, T. *Chem. Lett.* **1981**, 1135. (b) Sato, T.; Itoh, T.; Fujisawa, T. *Chem. Lett.* **1982**, 1559.
- (11) Grey, R. A. J. Org. Chem. 1984, 49, 2288.
- (12) (a) Tamaru, Y.; Ochiai, H.; Sanda, F.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *45*, 5529. (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *45*, 5559.
- (13) (a) Tokuyama, H.; Yokoshima, S.; Yamashita, T.;
 Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189. (b) Mori,
 Y.; Seki, M. *Tetrahedron Lett.* **2004**, *45*, 7343.
- (14) (a) Kneisel, F. F.; Dochnahl, M.; Knochel, P. Angew. Chem. Int. Ed. 2004, 43, 1017. (b) Wang, X.-J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. Org. Lett. 2005, 7, 5593.
- (15) Typical Procedure for Preparation of Alkylzinc Reagents

Under argon atmosphere, to a mixture of Zn metal (196 mg, 3.0 mmol) and DMI (0.43 mL, 4.0 mmol) in MeCN (3.0 mL)

was added one drop of TMSCl at 60 °C and stirred for 5 min, followed by addition of 2-phenylethyl iodide (0.43 mL, 3.0 mmol), stirring at the same temperature for 2 h, and cooling to r.t.

- (16) Toluene–DMI was utilized instead of benzene–DMA.
- (17) (a) Hasníl, Z.; Śilhár, P.; Hocek, M. *Synlett* 2008, 543.
 (b) Chekmarev, D. S.; Stepanov, A. E.; Kasatkin, A. N. *Tetrahedron Lett.* 2005, *46*, 1303.
- (18) Stylene was detected by GC-MS.
- (19) Typical Procedure for the Pd-Catalyzed Cross-Coupling Reaction

Under argon atmosphere, to a suspension of 6-chloronicotinoyl chloride (**1a**, 352 mg, 2.0 mmol) and Pd(phen)Cl₂ (21 mg, 0.06 mmol) in MeCN (3.0 mL) was added alkylzinc reagent **2** and stirring at same temperature. After stirring for 2 h, sat. NH₄Cl was added to the reaction mixture and extracted with EtOAc (2×20 mL). The combined EtOAc extract was washed with sat. NH₄Cl, sat. NaHCO₃ and brine, and dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by chromatography on SiO₂

(hexane–EtOAc, 6:1) to give the product 3a (453 mg, 92%) as white solid.

- Selected Spectra Data
- Compound **3a**: mp 82.9 °C. ¹H NMR (300 MHz, CDCl₃): $\delta = 8.91$ (1 H, d, J = 2.4 Hz), 8.16 (1 H, dd, J = 8.4, 2.4 Hz),
- 7.42 (1 H, d, J = 8.3 Hz), 7.32–7.18 (5 H, m), 3.31–3.26 (2 H, m), 3.10–3.05 (2 H, m). ¹³C NMR (75.5 MHz, CDCl₃): $\delta = 196.63, 155.44, 149.67, 140.43, 137.87, 130.84, 128.51,$ 128.27, 126.25, 124.41, 40.57, 29.60. IR (KBr): 3055, 3025, 1685, 1575, 1466, 1375, 1103, 700 cm⁻¹. MS (EI): *m/z* (relative intensity) = 245 (100) [M⁺], 140 (95). HRMS (EI): *m/z* calcd for C₁₄H₁₂ClNO [M⁺]: 245.0607; found: 245.0617. Compound 3f: white solid, mp 52.8 °C. ¹H NMR (300 MHz, $CDCl_3$): $\delta = 8.97 (1 H, d, J = 2.3 Hz), 8.21 (1 H, dd, J = 8.3, J)$ 2.4 Hz), 7.45 (1 H, d, J = 8.4 Hz), 4.16 (2 H, q, J = 7.1 Hz), 3.28 (2 H, t, J = 6.5 Hz), 2.79 (2 H, t, J = 6.4 Hz), 1.27 (3 H,t, J = 7.1 Hz). ¹³C NMR (75.5 MHz, CDCl₃): $\delta = 195.84$, 172.36, 155.68, 149.73, 137.93, 130.7, 124.49, 60.76, 33.58, 27.87, 14.10. IR (KBr): 3037, 2995, 1730, 1688, 1579, 1373, 1221 cm^{-1} . MS (EI): m/z (relative intensity) = 241 (31) [M⁺], 196 (65), 140 (100). HRMS (EI): m/z calcd for $C_{11}H_{12}CINO_3$ [M⁺]: 241.0506; found: 241.0504.
- (20) When excess amount of **2** (2.5 equiv) was used with $Pd(Ph_3P)_4$ catalyst, **4** and **6** were obtained in 45% and 38%, respectively.
- (21) (a) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. Org. Lett. 2007, 9, 4571. (b) Liu, J.; Deng, Y.; Wang, H.; Zhang, H.; Yu, G.; Wu, B.; Zhang, H.; Li, Q.; Marder, T. B.; Yang, Z.; Lei, A. Org. Lett. 2008, 10, 2661.

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