Biphenylphosphine-Palladium(II) Complexes-Catalyzed Friedel-Crafts Reaction for the Synthesis of α-Amino and α-Hydroxy Indolylacetates and Diindolylacetates

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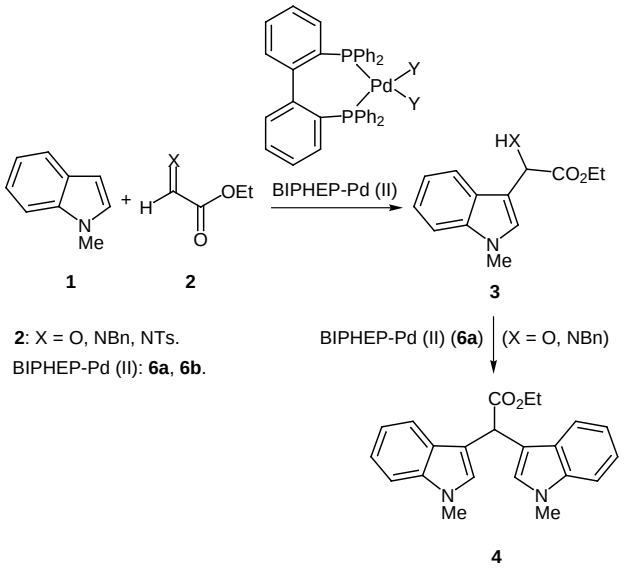
Abstract: Biphenylphosphine-palladium(II) complexes-catalyzed Friedel-Crafts reaction of *N*-methylindol with imino and carbonyl compounds afforded α-amino and α-hydroxy substituted indolylacetates and diindolylacetates in good yields.

Key words: biphenylphosphine, palladium complexes, Friedel-Crafts reaction, indoles

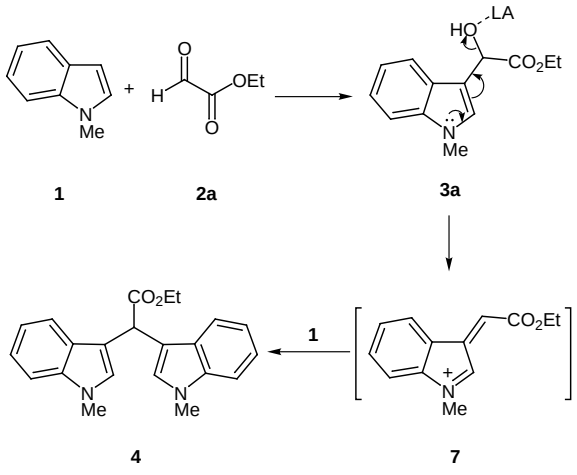
As one of the most important methodologies for carbon-carbon bond formation, the Friedel-Crafts reaction has been received great attention for several decades.[1] The Lewis acid catalyzed versions of alkylation and acylation reactions have been well developed in recent years.[2] However, the Friedel-Crafts additions of imines and aldehydes which would lead to the formation of α-amino and α-hydroxy acids of biological interests have not been well investigated yet.[3] Recent contribution by Johannsen for the asymmetric synthesis of indol α-amino acetic acid derivatives via $CuPF_6$-catalyzed Friedel-Crafts reactions of indol and *N*-tosyl imine has just been reported,[4] However, to the best of our knowledge, the palladium(II)-catalyzed Friedel-Crafts reaction of *N*-methylindole with glyoxylates, which would lead to the formation of α-hydroxy indolylacetates, has not been reported yet.

In our research on the transition metal-catalyzed glyoxylate-ene reaction, the palladium(II) species have been shown to give good catalytic activity.[5] This promoted us to further explore the possibility of palladium(II) catalysts in other carbon-carbon bond forming reactions. Herein, we report biphenylphosphine (BIPHEP)[6]- palladium(II) complexes-catalyzed Friedel-Crafts reaction of *N*-methylindole with glyoxylate and their imine counterparts, which give us an easy access to the biologically interesting molecules, such as α-hydroxy indolylacetates, α-amino indolylacetates, and diindolyl acetates (Scheme 1).

Our initial effort on $[Pd(CH_3CN)_2(BIPHEP)_2](SbF_6)_2$ (**6a**) catalyzed addition reaction of *N*-methylindole to glyoxylate at room temperature in dichloroethane was failed to give the α-hydroxy indolylacetates (**3a**) (Table, entry 2). Instead, the diindolyl acetate (**4a**) was obtained in 95% yield. The reaction should go through the α-hydroxy indolylacetate (**3a**), but the subsequent dehydroxylation and addition of another equivalent of indole rapidly took place to form the diindolylacetate. Dehydroxylation might arise from the high sensitivity of α-hydroxy indolylacetate (**3a**)



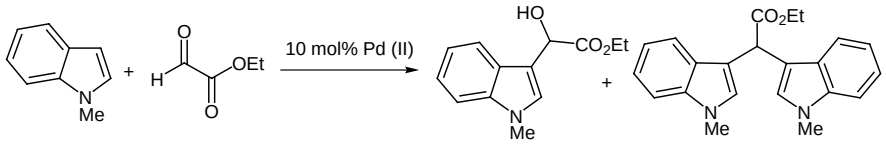
Scheme 1



Scheme 2

to the Lewis acid. 3-Alkylidene-*3H*-indolium cation **7** is considered to be formed during this reaction catalyzed by **6a**.[7] This intermediate is electrophilic enough to react with another equivalent of indole to form the diindolylacetate (**4**) in high yield (Scheme 2). Thus, we employed the neutral palladium(II) complex, such as $Pd(CH_3CN)_2Cl_2$ (**5**) and $Pd(BIPHEP)(OCOCF_3)_2$ (**6b**), instead of the cat-

Table Addition of *N*-Methyl-Indole to Ethyl Glyoxylate [8]



1 **2a** **3a** **4**

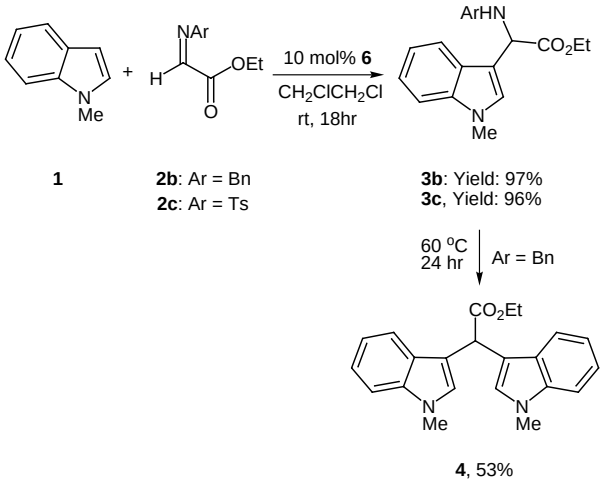
Entry	Pd (II)	Sol	Temp (°C)	Time (hr)	Yield (%)	
					3a	**4**
1	$Pd(CH_3CN)_2Cl_2$ (**5**)	CH_2ClCH_2Cl	rt	18	96	-
2	$[Pd(CH_3CN)_2(BIPHEP)](SbF_6)_2$ (**6a**)	CH_2ClCH_2Cl	rt	12	-	95
3	$[Pd(CH_3CN)_2(BIPHEP)](SbF_6)_2$ (**6a**)	CH_2Cl_2	-78 - rt	18	32	53
4	$[Pd(CH_3CN)_2(BIPHEP)](SbF_6)_2$ (**6a**)	Toluene	rt	18	52	28
5	$[Pd(CH_3CN)_2(BIPHEP)](SbF_6)_2$ (**6a**)	BTF[1]	rt	20	13	82
6	$Pd(BIPHEP)(OCOCF_3)_2$ (**6b**)	Toluene	rt	24	15	-
7	$Pd(BIPHEP)(OCOCF_3)_2$ (**6b**)	CH_2ClCH_2Cl	rt	24	45	-

[1]BTF = Benzotrifluoride

ionic complex (**6a**). The reaction was well controlled to offer **3a** in 96% yield in dichloroethane without observation of **4** (entry 1). It's worthy to mention that the product radio (**3a** vs **4**) is also affected by solvents and reaction temperature. Polar solvents, such as CH_2Cl_2 and CH_2ClCH_2Cl, provided good solubility to palladium complex **6a** and afforded the diindol product (**4**). Less polar solvent, such as toluene, provided the α-hydroxy indolylacetate **3a**. Lower reaction temperature could also reduce the possibility of dehydroxylation. For example, in the case catalyzed by the complex **6a**, α-hydroxy indolylacetate (**3a)** was obtained in 32% yield when the reaction was carried out from −78 °C to room temperature (entry 3). $Pd(BIPHEP)(OCOCF_3)_2$ also showed good selectivity to offer **3a** in dichloroethane at room temperature (entry 7).

Further investigation shows that this palladium(II)-catalyzed Friedel-Crafts reaction is also applicable to the imine counterparts. The $Pd(CH_3CN)_2Cl_2$ does not work well in this addition reaction of indole to *N*-benzyl imine at ambient temperature. It should be mentioned that the palladium cationic complex **6a** is effective to the less electrophlic imine, such as *N*-benzyl imine (Scheme 3).[9] Deamination followed by addition of one more equivalent of indole to form the diindolylacetate (**4**) was not observed when the reaction was carried out at room temperature. However, in the case of **2b**, deamination occurred when the reaction was carried out at 60 °C, and diindolylacetate **4** was obtained in 53% for 24 h. No deamination was observed in the case of **2c** even at 60 °C.

In summary, the biphenylphosphine-palladium(II)-catalyzed Friedel-Crafts reaction has been developed for the efficient synthesis of α-hydroxy indolylacetate, α-amino indolylacetate and diindolyl acetate.



Scheme 3

References and Notes

(1) Reviews: (a) Smith, M, B. *Organic Synthesis*; McGraw-Hill: New York, 1994; pp 1313. (b) Heaney, H. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 2, pp 733. (c) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry. A Century of Discovery*; Dekker: New York, 1984. (d) Olah, G. A. *Friedel-Crafts Chemistry*; Wiley-Interscience: New York, 1973.

(2) Reviews: (a) Yamamoto, H. *Ed*., *Lewis Acids in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, New York, London, Tokyo, 1996. (c) Mikami, K.; Nakai, T. Asymmetric Lewis Acid Catalysts. *Kagaku Zoukan* **1995,** *124*, 177. (d) Schinzer, D. *Selectivities in Lewis Acid Promoted Reaction*; Kluwer Academic Publishers: Dordrecht, Boston, London, 1988.

(3) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem. Int. Ed. Engl.* **1990,** *29*, 512. Also see: Ichii, A.; Kojima, J.; Mikami, K. *Org. Lett.* **1999**, *1*, 2013.
(4) Johannsen, M. *Chem. Commun*. **1999**, 2233.
(5) Hao, J.; Hatano, M.; Mikami, K. *Organic Lett.* **2000,** *2*, 4059.
(6) Chirally flexible biphenylphosphine (BIPHEP) ligands for catalytic asymmetric synthesis: Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem. Int. Ed*. **1999,** *38*, 495. Also see the use of this novel ligands: (a) BIPHEP-Ru complexes: Mikami, K.; Aikawa, K.; Korenaga, T. *Organic Lett.* **2000,** *2*, 0000. (b) BIPHEP-Pd complexes: Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000,** *19*, 1567. (c) BIPHEP-Pt complexes: Tudor, M. D.; Becker, J. J.; White, P. S.; Gagné, M. R. Organometallics **2000,** *19*, 4376.
(7) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry, 3rd Ed*.; Chapman & Hall, 1995, pp 312.
(8) General Procedure: To a solution of BIPHEP-Pd (II) complex (0.025 mmol, 10 mol% of ethyl glyoxylate) and 50 mg 4Å MS in 2 mL of dried solvent was added of ethyl glyoxylate (0.25 mmol in 2 mL dried solvent) and *N*-methyl indole (0.25 mmol to 0.50 mmol in 2 mL solvent) subsequently under the protection of argon atmosphere. This yellow solution was then stirred at certain reaction temperature for certain time, Reaction was monitored by TLC with elution of hexane/ethyl acetate = 2:1, solvent was then evaporated off by evaporator after reaction was finished, residue was purified by column chromatography with elution of hexane/ethyl acetate = 4/1 to afford the product as light yellow oil for **3a** and light pink oil for **4**. ^{1}H NMR ($CDCl_3$, 300 MHz) for **3a**: δ (ppm) = 1.24 (t, 3H, CH_3, J_{CH_3,CH_2} = 7.2 Hz), 3.30 (b, 1H, OH), 3.76 (s, 3H, NCH_3), 4.19 (dq, 2H, CH_2, J_{CH_2,CH_3} = 7.2 Hz), 5.45 (s, 1H, CH), 7.12 (s, 1H, 2-H), 7.14-7.73 (m, 4H, Ar). For **4**: δ (ppm) = 1.31 (t, 3H, CH_3, J_{CH_3,CH_2} = 7.2 Hz), 3.74 (s, 6H, NCH_3), 4.26 (q, 2H, CH_2, J_{CH_2,CH_3} = 7.2 Hz), 5.55 (s, 1H, CH), 7.06 (s, 2H, 2-H), 7.14-7.71 (m, 8H, Ar).
(9) ^{1}H NMR ($CDCl_3$, 300 MHz) for **3b**: δ (ppm) = 1.23 (t, 3H, CH_3, J_{CH_3,CH_2} = 7.2 Hz), 2.25 (b, 1H, NH), 3.76 (s, 3H, NCH_3), 3.84 (s, 2H, CH_2-Ph), 4.19 (dq, 2H, CH_2, J_{CH_2,CH_3} = 7.2 Hz), 4.71 (s, 1H, CH), 7.10 (s, 1H, 2-H), 7.12-7.72 (m, 9H, Ar). For **3c**: δ (ppm) = 1.12 (t, 3H, CH_3, J_{CH_3,CH_2} = 7.5 Hz), 2.35 (s, 3H, CH_3-Ph), 3.65 (s, 6H, NCH_3), 4.02 (dq, 2H, CH_2, J_{CH_2,CH_3} = 7.5 Hz), 5.32 (d, 1H, CH, $J_{CH\text{-}NH}$ = 8.4 Hz), 5.69 (d, 1H, NH, $J_{NH\text{-}CH}$ = 8.4 Hz), 6.92 (s, 1H, 2-H), 7.04-7.63 (m, 8H, Ar).

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