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First examples of a tosylate in the palladium-catalyzed Heck cross coupling reaction

Xiaoyong Fu,* Shuyi Zhang, Jianguo Yin, Timothy L. McAllister, S. Anna Jiang, Chou-Hong Tann, T. K. Thiruvengadam and Fucheng Zhang

Synthetic Chemistry Department, Schering-Plough Research Institute, 1011 Morris Ave. Union, NJ 07083, USA

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Abstract—The palladium-catalyzed cross coupling Heck reaction of tosylate (**2**) and methyl acrylate has been developed as an efficient method for carbon–carbon bond formation. The tosylate (**2**) was reacted with methyl acrylate using palladium acetate as catalyst to provide 3-(3-oxo-1-cyclohexen-1-yl)-2-propenoic acid methyl ester (**3**) in excellent yield. The coupling reaction of tosylate (**9**) under the similar conditions also provided the dienoic acid methyl ester (**10**) in >80% overall yield. The effect of reaction parameters such as temperature and catalyst as well as the ratio of palladium acetate to triphenylphosphine on the reaction rate has been studied.

The Heck coupling reaction is a well-known reaction to introduce carbon–carbon bonds at aryl or vinyl positions.[1] The utility of this reaction to prepare a variety of compounds from vinyl or aryl halides (bromides or iodides) and a vinyl compound in the presence of a palladium catalyst has been documented over the years.[2] Vinyl or aryl triflates, alternatives to halides, have been widely employed for Heck reaction due to their high reactivity. On the other hand, tosylate derivatives are generally considered to be unreactive in Heck cross coupling reactions, although tosylates have been reported as substrates in other transition metal-catalyzed coupling reactions. For example, Bolm et al. recently reported a successful synthesis of *N*-arylsulfoximes from aryl tosylate using $Ni(COD)_2$/BINAP catalyst.[3] The palladium-catalyzed Stille coupling reaction between tosylate derivatives and organostainanes has been studied and applied to the preparation of highly functionalized coumarin structures.[4] During the synthesis of 2-arylcarbapenem antibiotics, Huffman et al.[5] developed a coupling reaction between vinyl tosylates or phosphates derived from 1,3-dicarbonyl compounds and phenylboronic acid using Ni or Pd catalysts. This procedure offered an efficient and low cost alternative to vinyl triflates for cross coupling reaction with arylboronic acids. However, to our knowledge, tosylates have not been reported as substrates in the Heck cross coupling reactions. We wish to report here the first example of the palladium-catalyzed Heck protocol using vinyl tosylates as alternatives to vinyl triflates and vinyl bromides, and the successful application of this reaction in the cost effective preparation of Himbacine analog building blocks.[6]

We envisioned that compound **3** can be efficiently constructed via a Heck reaction of methyl acrylate with the vinyl bromide or vinyl triflate derived from the corresponding cyclohexane-1,3-dione (**1**). However, preparation of the bromide requires extra steps including conversion of the dione into mesylate or tosylate followed by substitution with bromide.[7] Triflate is synthesized using expensive reagent, which is not cost effective for large-scale preparation. On the other hand, the vinyl tosylate, if works, would offer substantial advantages such as its ease of preparation, handling and work up as well as low cost of the needed reagents to prepare it. We decided to explore the possibility.

The tosylate **2** was prepared based on a reported method[8] by reacting cyclohexane-1,3-dione with tosylchloride in the presence of triethylamine. The tosylate **2** can be isolated by conventional aqueous work up followed by crystallization in EtOAc and heptane. When the isolated tosylate solid was subjected to the Heck cross coupling conditions with methyl acrylate using bistriphenylphosphine palladium chloride (5 mol%) as catalyst and a mixture of DMF and DMA as solvent in the presence of TEA at about 95°C, the methyl ester **3** was formed as a predominating product.

Keywords: tosylate; Heck cross coupling.

* Corresponding author. Fax: (908)820-6620; e-mail: xiaoyong.fu@spcorp.com

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With this unexpected, yet very promising result, our attention was directed toward optimizing the reaction parameters.

The isolated tosylate **2** is not very stable and it partially decomposes into a dark colored material when standing at room temperature overnight. It would be prudent to combine the tosylate formation and Heck coupling into a single step. Indeed, when the dione was reacted with TsCl in DMF and in the presence of triethylamine, tosylate **2** was cleanly formed in about 1 h; and subsequent coupling with methyl acrylate provided the desired product in >60% yield by HPLC. However, more impurities were generated from this one pot procedure. The major impurity was identified as 3-chloro-2-cyclohexene-1-one,[9] which was confirmed by an independent preparation from a substitution of tosylate with lithium chloride. Therefore, it is crucial to control the amount of TEA hydrochloride before the coupling reaction. Taking advantage of low solubility of TEA hydrochloride in toluene, it was decided to filter off the salt from the reaction mixture once the tosylation was complete. Toluene was replaced with DMF by vacuum concentration to provide the tosylate solution for the coupling. A clean product was formed.

The catalyst bistriphenylphosphine palladium chloride was replaced with the less expensive palladium acetate and triphenylphosphine. The ratio of palladium and triphenylphosphine is crucial to the reaction rate (Table 1).

Although a combination of 2–4 equiv. of triphenylphosphine and palladium acetate has been commonly employed in the traditional Heck reaction,[10] the catalyst was completely inactive when 3 equiv. of PPh_3 was used for the conversion of **2** to **3** (entry 1) (Scheme 1). However, in the absence of the ligand (PPh_3), reaction only proceeded to a certain extent when the catalyst was fully decomposed. Addition of triphenylphosphine at this point would not revive the catalyst and the catalysis would only resume when fresh palladium acetate was introduced to the reaction mixture (entry 2). Further experiments with different combination ratios of $Pd(OAc)_2$ and PPh_3 were conducted for this catalysis. The results from Table 1 (entries 3–6) clearly demonstrated that the most active catalyst was generated when a $\sim$1:1 ratio of $Pd(OAc)_2$ and PPh_3 was used for the reaction. This unexpected finding appeared to be contradictory to the active species $Pd^0(PPh_3)_2(OAc)^-$ recently reported by Amatore et al.[11]

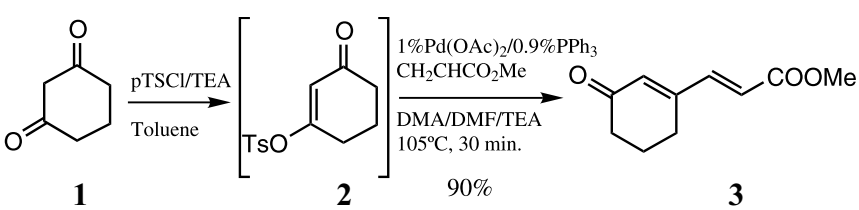
The catalyst loading could be reduced to about 0.1 mol%. However, the reaction was not very clean with a long reaction time (entry 9) due to the product instability under the reaction conditions. The reaction temperature was also examined. At lower temperature (below 90°C) it took much longer time to complete the transformation. In consequence, impurities were generated at higher level and the yield was lowered. The reaction was best performed at a temperature of about 105°C to ensure a cleaner and higher yield process. The optimized process has been successfully scaled up to multi kg in the production with reproducible high yield ($\sim$90%) and quality. The ester **3** has been further transformed to a himbacine analog and will be reported in the due course.

The scope of this tosylate Heck reaction was extended to other vinyl compounds (Fig. 1). Reaction of **2** with

Table 1. Reaction dependence on ratio of palladium acetate and triphenylphosphine

Entry	Equiv. $Pd(OAc)_2$	Equiv. PPh_3	Time	Conv. (%)	HPLC (area %)
1	0.015	0.045	3 h	0	No rxn
2	0.045	0	4.5 h	46.5	34.1
		0.020	2 h	48.4	37.3
	+0.016		1 h	95.4	75.5
3	0.015	0.020	1 h	100.0	89.6
4	0.015	0.015	10 min	100.0	94.6
5	0.015	0.0075	3 h	98.0	86.6
6	0.015	0.003	5 h	84.3	74.4
7	0.010	0.009	30 min	100.0	95.7
8	0.005	0.0045	2.5 h	100.0	94.6
9	0.0011	0.0011	47 h	99.1	69.9

Equiv. denotes mol equivalence of each reagent relative to 1,3-cyclohexanedione. Reaction time denotes the agitation time after the batch was heated to 100–110°C. Conv. (%) denotes the ratio of product over the sum of product and starting material by HPLC analysis.



Scheme 1. One-pot preparation of **3**.

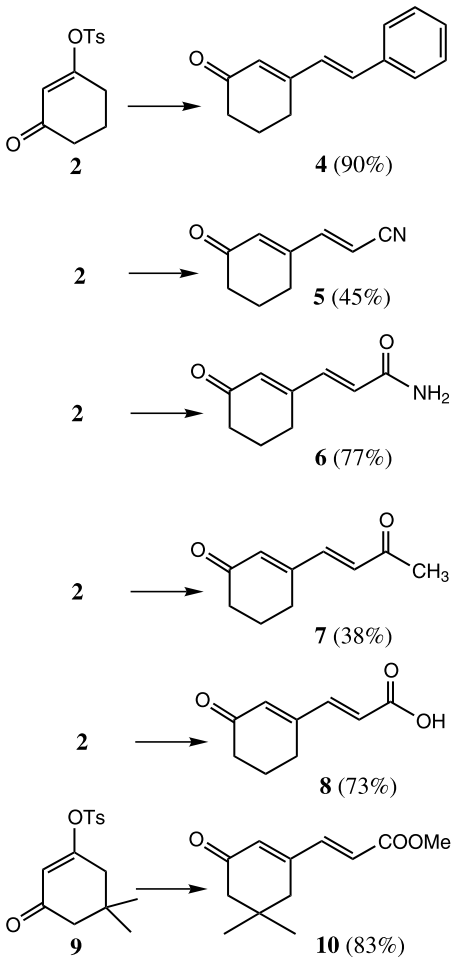


Figure 1. Tosylate Heck reactions.[14]

styrene provided an efficient synthesis for 3-styryl-2-cyclohexen-1-one (**4**)[12] in 90% overall yield from **1**, which was normally prepared by multiple step preparations in low to moderate yields.[13] However, coupling of **2** with acrylonitrile only provided **5** in about 45% solution yield, presumably due to its low stability under the reaction conditions. Generally, all tosylates derived from cyclic β-diketones can be used for this coupling (Fig. 1). Mesylate derived from cyclohexane-1,3-dione can also be employed but the yield was significantly lower. It is presumably due to its lower stability than the corresponding tosylate. Further studies are necessary to understand this special reaction.

General experimental procedures: To a 1-L 3-necked round bottom flask equipped with a thermometer, a mechanical stirrer and nitrogen, 30.0 g (267.6 mmol) of 1,3-cyclohexandione **1**, 51.0 g (1 equiv.) of *p*-toluenesulfonyl chloride and 300 ml of toluene were mixed and slurred at room temperature. 49 ml (1.3 equiv.) of triethylamine was slowly introduced via addition funnel while maintaining the reaction temperature to between 20 and 30°C. The mixture was further agitated at 20–25°C and filtered upon the completion of the reaction (<1% of **1**) as followed by HPLC (Waters HPLC with PDA module, isocratic mobile phase composed of 50:50 water and acetonitrile, μ-Boundpak C-18 column; UV 254 nm). The filtrate (**2**) was concentrated under reduced pressure, followed by solvent replacement with *N*,*N*-dimethylacetamide to a volume of about 120 ml. With 700 mg (2.67 mmol) of triphenylphosphine, 600 mg (2.67 mmol) of palladium (II) acetate, *N*,*N*-dimethylformamide (60 ml), triethylamine (60 ml), *N*,*N*-dimethylacetamide (30 ml) and 36.4 ml (1.5 equiv.) of methyl acrylate charged, the mixture was heated to 100–110°C and stirred for 30 min. Following the completion of the reaction that was monitored by HPLC, the reaction mixture was cooled, diluted with 300 ml of toluene, 240 ml of water and acidified with HCl to a pH <4. The aqueous layer was separated and extracted twice with toluene (150 ml each). The combined organic layer was washed with water (150 ml), brine (150 ml) and concentrated under reduced pressure to 120 ml. Further treatment with silica gel (15 g), activated carbon (3 g) and Celite (3 g) afforded a clean product solution with a yield of 90%, upon filtration. With solvent evaporated, the analytically pure product **3** was obtained by recrystallization from a 50 ml/50 ml ethyl acetate/*n*-heptane mixture as a white crystalline powder.

In summary, the palladium-catalyzed Heck cross coupling of tosylate derived from β-diketone with methyl acrylate has been discovered as an efficient and cost effective methodology for constructing himbicine analogues building block. The reaction parameters, especially the ratio of palladium acetate and triphenylphosphine have been found to be critical to the reaction rate and a 1:1 combination of the two components was proven to generate the most active catalyst for this transformation.

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14. Overall isolated yield from the corresponding dione. ^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9** and **10** are summarized below.
For compound **2**: ^{1}H NMR ($CDCl_3$): 7.83 (doublet of triplet, 1H, $J=8.5$, 1.8 Hz), 7.39 (d, 2H, $J=8.0$ Hz), 5.80 (t, 1H, $J=1.2$ Hz), 2.49 (m, 5H), 2.32 (t, 2H, $J=6.4$ Hz), 2.00 (m, 2H). ^{13}C NMR ($CDCl_3$): 199.1, 168.7, 146.6, 132.8, 130.6, 128.6, 117.2, 36.8, 29.0, 22.2, 21.2.
For compound **3**: ^{1}H NMR ($CDCl_3$): 7.35 (d, 1H, $J=16.0$ Hz), 6.25 (d, 1H, $J=16.0$ Hz), 6.15 (s, 1H), 3.80 (s, 3H), 2.47 (m, 4H), 2.10 (m, 2H). ^{13}C NMR ($CDCl_3$): 199.5, 166.2, 153.6, 144.5, 132.6, 123.7, 52.0, 37.6, 24.7, 22.0. HRMS (M+1), calcd for $C_{10}H_{13}O_3$, 181.0865. Found: 181.0862. Elemental analysis: calcd for $C_{10}H_{12}O_3$, C, 66.65; H, 6.71. Found: C, 66.76; H, 6.70.
For compound **4**: ^{1}H NMR ($CDCl_3$): 7.53 (d, 2H, $J=7.8$ Hz), 7.38 (m, 3H), 7.03 (d, 1H, $J=16.2$ Hz), 6.91 (d, 1H, $J=16.3$ Hz), 6.10 (s, 1H), 2.64 (t, 2H, $J=6.0$ Hz), 2.49 (t, 2H, $J=6.2$ Hz), 2.12 (m, 2H). ^{13}C NMR ($CDCl_3$): 200.6, 157.4, 136.4, 135.6, 129.8, 129.5, 129.3, 128.6, 127.7, 38.1, 25.4, 22.7.
For compound **5**: ^{1}H NMR ($CDCl_3$): 7.16 (dd, 1H, $J=16.5$, 0.4 Hz), 6.15 (s, 1H), 5.78 (dd, 1H, $J=16.5$, 0.5 Hz), 2.48 (m, 4H), 2.13 (m, 2H). ^{13}C NMR ($CDCl_3$): 199.5, 152.3, 151.0, 133.3, 117.3, 102.8, 37.9, 24.4, 22.2.
For compound **6**: ^{1}H NMR (DMSO): 7.74 (s, 1H), 7.29 (s, 1H), 7.17 (d, 1H, $J=15.8$ Hz), 6.52 (d, 1H, $J=15.7$ Hz), 6.13 (s, 1H), 2.46 (t, 2H, $J=5.8$ Hz), 2.36 (t, 2H, $J=6.2$ Hz), 1.97 (m, 2H). ^{13}C NMR (DMSO): 200.1, 166.7, 156.0, 140.3, 131.4, 129.3, 38.1, 25.2, 22.6.
For compound **7**: ^{1}H NMR ($CDCl_3$): 7.19 (d, 1H, $J=16.2$ Hz), 6.49 (d, 1H, $J=16.2$ Hz), 6.21 (s, 1H), 2.49 (m, 4H), 2.37 (s, 3H), 2.10 (m, 2H). ^{13}C NMR ($CDCl_3$): 199.9, 198.2, 154.5, 143.2, 133.5, 132.3, 38.1, 28.1, 25.2, 22.4.
For compound **8**: ^{1}H NMR (DMSO): 12.71 (broad s, 1H), 7.34 (d, 1H, $J=15.9$ Hz), 6.33 (d, 1H, $J=15.9$ Hz), 6.23 (s, 1H), 2.51 (t, 2H, $J=6.0$ Hz), 2.36 (t, 2H, $J=6.7$ Hz), 1.96 (m, 2H). ^{13}C NMR (DMSO): 200.2, 167.7, 155.4, 144.8, 132.5, 126.1, 38.1, 25.0, 22.6.
For compound **9**: ^{1}H NMR ($CDCl_3$): 7.75 (dd, 2H, $J=6.6$, 1.7 Hz), 7.31 (d, 2H, $J=8.0$ Hz), 5.70 (t, 1H, $J=1.2$ Hz), 2.40 (s, 3H), 2.32 (d, 2H, $J=1.2$ Hz), 2.13 (s, 2H), 0.96 (s, 6H). ^{13}C NMR ($CDCl_3$): 199.2, 167.1, 146.6, 132.8, 130.5, 128.7, 116.4, 50.9, 42.9, 33.3, 28.4, 22.2.
For compound **10**: ^{1}H NMR ($CDCl_3$): 7.42 (d, 1H, $J=15.9$ Hz), 6.29 (d, 1H, $J=15.9$ Hz), 6.20 (s, 1H), 3.82 (s, 3H), 2.37 (s, 2H), 2.34 (s, 2H), 1.15 (s, 6H). ^{13}C NMR ($CDCl_3$): 200.2, 166.7, 151.9, 145.1, 132.0, 123.9, 52.4, 51.7, 33.7, 28.7. HRMS (M+1) calcd for $C_{12}H_{17}O_3$, 209.1178, Found: 209.1178. Elemental analysis: calcd for $C_{12}H_{16}O_3$, C, 69.21; H, 7.74. Found: C, 69.18; H, 7.70.