

# The First Thiadiazolidine 1-Oxide System for Phosphine-Free Palladium-Mediated Catalysis

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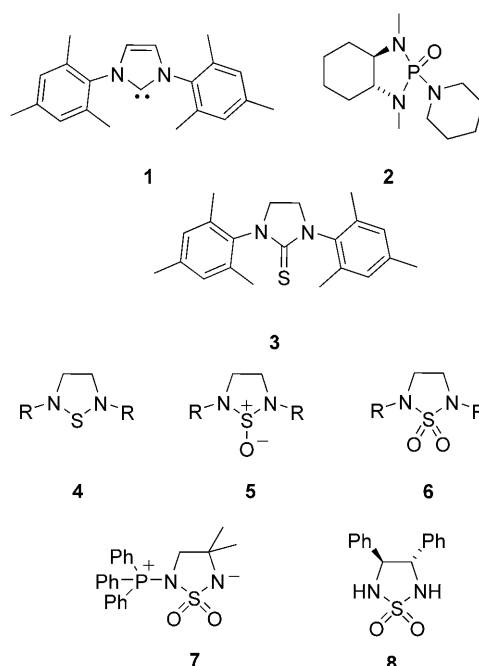
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**Abstract:** We herein report a highly active catalyst system using for the first time a thiadiazolidine 1-oxide as a ligand for palladium in the Mizoroki–Heck reaction. Excellent yields of stilbenes derived from aryl iodides and bromides have been achieved using as little as 0.00002 mol% catalyst. The ligand/palladium system can be stored as a stock solution open to air at room temperature with no observable loss of activity for a period of several weeks/months.

**Keywords:** catalysis; C–C coupling; Mizoroki–Heck reaction; palladium; thiadiazolidines

There are a wide number of reports utilizing a 1,3-nitrogen skeleton as a basis for catalyst/ligand design; for example, N-heterocyclic carbenes **1**,<sup>[1]</sup> phosphoramides **2**,<sup>[2]</sup> and thioureas **3**.<sup>[3]</sup> Indeed 1,3-amines and imines have themselves been reported as ligands and catalysts. However, there are very few reports regarding the synthesis of structurally related thiadiazolidines **4** or thiadiazolidine oxides **5**. The majority of reports regarding thiadiazolidine 1,1-dioxides **6** relate to their pharmacological properties,<sup>[4]</sup> the zwitterion **7** has been used in a Mitsunobu-type reaction<sup>[5]</sup> and **8** has been proposed in connection with Oppolzer's sultam model.<sup>[6]</sup> Thiadiazolidine 1,1-dioxides have also been reported as useful polar aprotic solvents<sup>[7]</sup> and as key intermediates for the synthesis of constrained peptides.<sup>[8]</sup> We were particularly attracted to the thiadiazolidine oxides as we postulated that they may be interesting and useful ligands for metal-catalysed reactions.

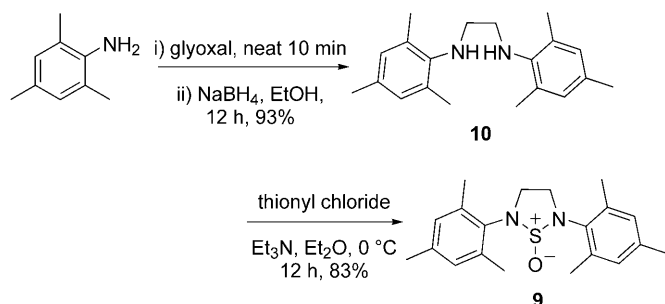
Traditionally, phosphine ligands have been used to stabilise reactive palladium intermediates, and excellent results have been reported for Pd-catalysed Mizoroki–Heck reactions.<sup>[9,10,11]</sup> Sterically bulky mono-



phosphines,<sup>[12]</sup> diphosphines,<sup>[13]</sup> cyclometallated phosphines, and phosphites are particularly good ligands for palladium.<sup>[14,15]</sup> The air-sensitivity of these types of ligands, however, precludes their use in a variety of synthetic applications. Therefore, the development of phosphine-free palladium catalysis is a topic of enormous interest,<sup>[16]</sup> with thioureas being amongst the most effective systems.<sup>[3,17,18]</sup> In our continuing programme for the development of nitrogen-sulfur-oxygen ligands/catalysts we herein report the first use of an air-stable thiadiazolidine oxide in the Mizoroki–Heck reaction.

We conjectured that thiadiazolidine 1-oxides might be effective ligands for palladium-mediated processes, and in order to test our hypothesis we chose to prepare the mesityl-derived thiadiazolidine oxide **9**. This was easily achieved in two steps; mesitylamine and

glyoxal were reacted neat, and upon formation of the bright yellow bis-imine, sodium borohydride/ethanol was added to furnish the bis-amine **10** in excellent yield (Scheme 1). Treatment of a solution of **10** in di-

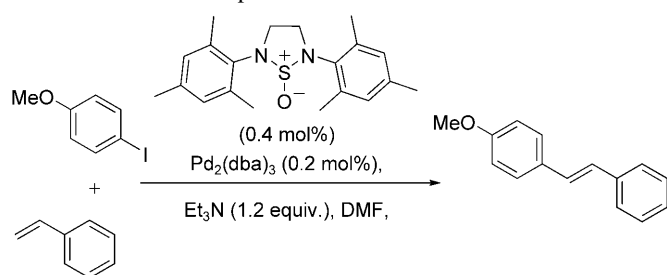


**Scheme 1.**

ethyl ether/triethylamine with thionyl chloride afforded the thiadiazolidine oxide **9** in good yield.

With ligand **9** in hand we chose to screen a range of palladium sources, using 4-methoxyiodobenzene and styrene, as our test system, and carried out the reactions under microwave irradiation.<sup>[19]</sup> We found that the system reported by Yang was particularly applicable, and we eventually chose Pd<sub>2</sub>(dba)<sub>3</sub> as our standard source of palladium.<sup>[3]</sup> Optimisation of the microwave system revealed that reactions could be effectively carried out at 150 °C in 10 min with 0.2 mol% of Pd<sub>2</sub>(dba)<sub>3</sub> and 0.4 mol% of the ligand (Table 1). Reactions carried out at 200 °C for only 1 min afforded 85% of the desired product. For convenience we settled on a reaction time of 10 min and

**Table 1.** Microwave optimization studies.<sup>[a]</sup>



| Entry | Temp [°C] | Time [min] | Conversion [%] <sup>[b]</sup> |
|-------|-----------|------------|-------------------------------|
| 1     | 100 °C    | 10 min     | < 5%                          |
| 2     | 150 °C    | 10 min     | 100%                          |
| 3     | 200 °C    | 10 min     | 100%                          |
| 4     | 200 °C    | 1 min      | 85%                           |

<sup>[a]</sup> Standard conditions: Pd<sub>2</sub>(dba)<sub>3</sub> (0.2 mol%), **9** (0.4 mol%), Et<sub>3</sub>N (1.2 equiv), DMF (0.5 mL), *T* °C, in a Biotage Initiator Microwave.

<sup>[b]</sup> Conversions were evaluated using <sup>1</sup>H NMR spectroscopy, by comparison of the methoxy protons from 4-iodoanisole and the product.

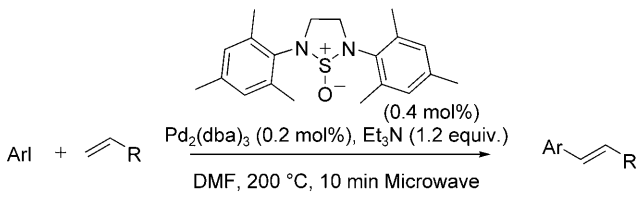
a temperature of 200 °C (reactions of other substrates at 150 °C resulted in slightly lower yields when compared to the corresponding reaction at 200 °C). Using our optimised conditions, we went on to screen a range of substrates, and were delighted to find that excellent yields of the corresponding styrenes and α,β-unsaturated esters could be achieved in reaction times of only 10 min (Table 2). We have observed that the reactions are tolerant of both electron-donating and withdrawing substituents on either the aryl iodide or the alkene components, with yields generally of over 95%. For reasons which are unclear at present the reaction of methyl acrylate and iodobenzene (Table 2, entry 6) was extremely capricious and over several runs the yield of product varied significantly (28–81%). Although these reactions were carried out under microwave irradiation, we also confirmed that these reactions can take place under more conventional thermal conditions. The Heck reaction of butyl acrylate and iodobenzene achieved complete conversion within two hours using standard reflux conditions.

For convenience, stock catalyst solutions of the palladium/ligand complex were prepared and we were surprised to find that the prepared ligand/palladium complex is extremely air- and moisture-tolerant and can be stored for months as a stock solution in DMF or NMP open to air at room temperature with no observable loss of activity (a similar observation for thiourea systems has been reported by Yang<sup>[3]</sup>).<sup>[20]</sup> This is in stark contrast to a range of phosphine ligands that have to be prepared and used under strict inert reaction conditions and, therefore, precludes their effective use in industrial applications.

Following the work on aryl iodides, Heck reactions were attempted using aryl bromides as substrates (Table 3). The conditions used for aryl iodides were found to be unsuitable for aryl bromides. The solvent was changed from DMF to *N*-methylpyrrolidinone (NMP), and sodium acetate was used as the base. Some reactions performed at 200 °C were prone to excess pressure build-ups inside the sealed vials used for irradiation. In these cases, the reaction temperatures were reduced to 160 °C. Pd(dba)<sub>2</sub> was used as the palladium source and reaction times were extended to 30 min.

Over the course of the initial experiments, with the bromide-Heck reactions, only two were ever safely brought to 200 °C without incident, the reactions of bromobenzene with styrene (Table 3 entry 1) and with butyl acrylate (Table 3 entries 4 and 5). Any attempts to bring reactions involving substituted aryl bromides, substituted styrenes or methyl acrylate to 200 °C in the microwave resulted in shattering of the sealed vial. Lowering of the temperature to below 170 °C prevented shattering of the vial but also resulted in a low yield.

**Table 2.** Heck reactions using palladium and ligand **9**.<sup>[a]</sup>

|  |             |        |         |                          |
|------------------------------------------------------------------------------------|-------------|--------|---------|--------------------------|
| Entry                                                                              | Aryl Iodide | Alkene | Product | Yield [%] <sup>[b]</sup> |
| 1                                                                                  |             |        |         | 97%                      |
| 2                                                                                  |             |        |         | 99%                      |
| 3                                                                                  |             |        |         | 99%                      |
| 4                                                                                  |             |        |         | 99%                      |
| 5                                                                                  |             |        |         | > 99%                    |
| 6                                                                                  |             |        |         | up to 81% <sup>[c]</sup> |
| 7                                                                                  |             |        |         | 97%                      |
| 8                                                                                  |             |        |         | 99%                      |
| 9                                                                                  |             |        |         | 93%                      |
| 10                                                                                 |             |        |         | 99%                      |
| 11                                                                                 |             |        |         | 98%                      |

<sup>[a]</sup> Standard conditions: Pd<sub>2</sub>(dba)<sub>3</sub> (0.2 mol%), **9** (0.4 mol%), Et<sub>3</sub>N (1.2 equiv), DMF (0.5 mL), 200 °C, 10 min in a Biotage Initiator Microwave.

<sup>[b]</sup> Isolated yield over an average of 3 runs.

<sup>[c]</sup> Capricious reaction: variable yields over 3 runs: 28%, 50% and 81%.

**Table 3.** Heck reactions of aryl bromides.<sup>[a]</sup>

| Entry            | R | Alkene | Temp. [°C] | Time [min] | Yield [%] <sup>[b]</sup> |
|------------------|---|--------|------------|------------|--------------------------|
| 1                |   |        | 200        | 30         | 99%                      |
| 2 <sup>[c]</sup> |   |        | 160        | 30         | 85%                      |
| 3 <sup>[c]</sup> |   |        | 160        | 30         | 85%                      |
| 4                |   |        | 200        | 30         | 14                       |
| 5                |   |        | 200        | 180        | 28                       |
| 6 <sup>[c]</sup> |   |        | 160        | 30         | N.R.                     |
| 7 <sup>[c]</sup> |   |        | 160        | 30         | 27                       |
| 8 <sup>[c]</sup> |   |        | 160        | 30         | 24                       |

<sup>[a]</sup> Standard conditions: Pd(dba)<sub>2</sub> (0.1 mol%), **9** (0.4 mol%), NaOAc (1.2 equiv), NMP (0.5 mL), *T* °C, in a Biotage Initiator Microwave.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> Reaction vial shattered at temperatures above 180 °C.

In light of this, Heck reactions using bromides were attempted using conventional heating under reflux conditions. In these cases, temperatures exceeding 180 °C resulted in a complex mixture of products. Keeping temperatures below 150 °C was sufficient to achieve crude yields consisting only of the expected product and its starting materials. Unfortunately the isolated product yields were still low (Table 4).

However, we have found that the addition of tetrabutylammonium bromide (TBAB) to the reactions has allowed them to proceed smoothly at 200 °C in the microwave apparatus. The synthesis of various stilbene products with both electron-donating and -withdrawing groups is possible in excellent yields. The addition of TBAB has also made it possible to increase the yield of the reaction of bromobenzene and butyl acrylate to 73% (Table 5, entry 5).

After successful conversion of these aryl bromides and iodides to stilbene products we turned our attention to the effectiveness of this ligand system over a

**Table 4.** Heck reactions performed by conventional reflux.<sup>[a]</sup>

| Entry | R | Alkene | Temp. [°C] | Time [h] | Yield [%] <sup>[b]</sup> |
|-------|---|--------|------------|----------|--------------------------|
| 1     |   |        | 200        | 24       | complex mixture          |
| 2     |   |        | 140        | 24       | 37%                      |
| 3     |   |        | 140        | 24       | 18%                      |

<sup>[a]</sup> Standard conditions: Pd(dba)<sub>2</sub> (0.1 mol%), **9** (0.4 mol%), NaOAc (1.5 equiv), NMP (0.5 mL), *T* °C.

<sup>[b]</sup> Isolated yield.

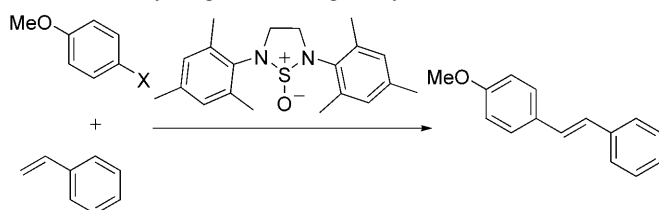
**Table 5.** Heck reactions of aryl bromides in the presence of TBAB under microwave conditions.<sup>[a]</sup>

| Entry | R | Alkene | Temp. [°C] | Time [min] | Yield [%] <sup>[b]</sup> |
|-------|---|--------|------------|------------|--------------------------|
| 1     |   |        | 200        | 30         | 99%                      |
| 2     |   |        | 200        | 30         | 99%                      |
| 3     |   |        | 200        | 30         | 98%                      |
| 4     |   |        | 200        | 30         | 89%                      |
| 5     |   |        | 200        | 30         | 73%                      |

<sup>[a]</sup> Standard conditions: Pd(dba)<sub>2</sub> (0.1 mol%), **9** (0.8 mol%), NaOAc (1.5 equiv), NMP (0.5 mL), TBAB (0.4 equiv), *T* °C, in a Biotage Initiator Microwave.

<sup>[b]</sup> Isolated yield.

range of catalyst loadings (Table 6). Our experiments have shown that the system was still effective at extremely low catalyst loadings; for lower loadings the

**Table 6.** Catalyst/ligand loading study.<sup>[a]</sup>

| Entry | X  | Pd [mol%] | <b>9</b> [mol%] | Time    | TON       | Conv. [%] <sup>[b]</sup> |
|-------|----|-----------|-----------------|---------|-----------|--------------------------|
| 1     | I  | 0.2       | 0.4             | 10 min  | 485       | 97                       |
| 2     | I  | 0.02      | 0.04            | 10 min  | 5000      | 100                      |
| 3     | I  | 0.002     | 0.004           | 10 min  | 29,000    | 58                       |
| 4     | I  | 0.002     | 0.004           | 30 min  | 48,500    | 97                       |
| 5     | I  | 0.0002    | 0.0004          | 10 min  | 160,000   | 32                       |
| 6     | I  | 0.0002    | 0.0004          | 30 min  | 205,000   | 41                       |
| 7     | I  | 0.0002    | 0.0004          | 60 min  | 490,000   | 98                       |
| 8     | I  | 0.00002   | 0.00004         | 30 min  | 1,050,000 | 21                       |
| 9     | Br | 0.0001    | 0.0008          | 30 min  | 600,000   | 60                       |
| 10    | Br | 0.0001    | 0.0008          | 60 min  | 640,000   | 64                       |
| 11    | Br | 0.0001    | 0.0008          | 120 min | 740,000   | 74                       |

<sup>[a]</sup> Standard conditions for aryl iodides: Pd<sub>2</sub>(dba)<sub>3</sub>, **9**, Et<sub>3</sub>N (1.2 equiv.), DMF (0.5 mL), 200 °C, in a Biotage Initiator Microwave; standard conditions for aryl bromides: Pd(dba)<sub>2</sub> (0.1 mol%), **9** (0.8 mol%), NaOAc (1.5 equiv.), NMP (0.5 mL), TBAB (0.4 equiv.), 200 °C.

<sup>[b]</sup> Conversions were evaluated using <sup>1</sup>H NMR spectroscopy, by comparison of the methoxy protons from 4-iodoanisole or 4-bromoanisole and the product.

reaction times could be extended to give conversions >95% (aryl iodides). After some optimisation it appears that we can achieve highly effective conversions to the stilbenes from 4-iodoanisole (98%) and 4-bromoanisole (79%) with as little as 0.0002 mol% palladium and 0.0004/0.0008 mol% of the ligand (TON of 490,000 and 740,000, respectively). Although low conversions can be somewhat increased by irradiating for a second or third time in the microwave reactor, it is far more effective to irradiate the reaction mixture for a longer single run.

The activity of our system appears to be highly dependent on the presence of anionic ligands for palladium, like halide or acetate ions. The “halide effect” has been thoroughly studied by, for example, Amatore and Jutand.<sup>[21]</sup> Computational studies of the effects of halides or acetates have been published by Shaik<sup>[22]</sup> and by Norrby.<sup>[23]</sup> Some very interesting results showing high activity of palladium in the presence of acetate anions were published by Reetz<sup>[24]</sup> and by de Vries.<sup>[25]</sup> In view of these reports, we decided to run the same experiments in the absence of any ligand, as it is plausible that the active palladium species does not contain the ligand. However, when using 1 mol% Pd systems for the conversion of aryl iodides and aryl bromides in the absence of ligand **9**

we observed a maximum of up to 40% conversion to the desired Heck product (compared to 76% conversion when using the ligand **9**). Indicating that the active catalytic species must require the ligand for high turnover and product yield.

In summary, we have developed a highly active, easily prepared and air-stable thiadiazolidine 1-oxide ligand, which in conjunction with palladium effectively catalyses the Mizoroki–Heck reaction of activated and unactivated iodides and bromides. Remarkably, the prepared ligand/palladium complex can be stored (months) as a stock solution in DMF or NMP open to air at room temperature with no observable loss of activity. Further investigations into the ligand structure to identify an even more reactive system are currently in progress as is the development of these systems for other metal-catalysed reactions.

## Experimental Section

### General Procedure for the Mizoroki–Heck Reaction using Aryl Iodides

Pd<sub>2</sub>(dba)<sub>3</sub> (2.3 mg, 0.0025 mmol) and **9** (4 equiv.) were stirred in DMF (0.5 mL) for 0.5 h at room temperature. Iodobenzene (0.28 mL, 2.5 mmol, substrate/catalyst ratio = 500:1) and styrene (0.32 g, 3.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) were then added. The flask was crimped and heated at 200 °C under microwave irradiation for 10 min. After the indicated time, the solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under reduced pressure and the product isolated by crystallisation from dichloromethane/diethyl ether or by flash column chromatography.

### General Procedure for the Mizoroki–Heck Reaction using Aryl Bromides

Pd(dba)<sub>2</sub> (1.5 mg, 0.0025 mmol), ligand (**9**, 8 equiv.), TBAB (1 mmol) and sodium acetate (0.33 g, 3.8 mmol) were stirred in NMP (1.5 mL) for 1 h at room temperature. Aryl bromide (2.5 mmol, substrate/catalyst ratio = 1000:1) and olefin (2.5 mmol) were then added. The flask was crimped and heated at 200 °C under microwave irradiation for 30 min. After the indicated time, the solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under reduced pressure. The product was isolated by flash column chromatography.

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