The first examples of the enantioselective Heck–Matsuda reaction: arylation of unactivated cyclic olefins using chiral bisoxazolines

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A R T I C L E   I N F O

Article history:
Received 31 March 2012
Revised 16 April 2012
Accepted 17 April 2012
Available online 24 April 2012

Keywords:
Enantioselective Heck–Matsuda
Bisoxazolines
Arenediazonium salts

A B S T R A C T

Successful enantioselective Heck–Matsuda arylations were accomplished for the first time using chiral bisoxazolines as ligands. Enantioselective Heck arylations were performed with several cyclic nonactivated olefins to provide the Heck products in 63–96% isolated yields and in enantiomeric excesses of 54% up to 84%.

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Introduction

Enantioselective catalysis has revolutionized the field of organic synthesis and brought huge benefits for society in general. For example, the development of enantioselective catalysis provides more selective and less toxic therapeutic drugs, fragrances and new materials. Additionally, the development of effective and practical catalytic methods, which carry economical and ‘greener’ aspects, has been a topic of great interest in recent years. In this context, palladium catalyzed coupling of arenediazonium salts to olefins (Heck–Matsuda reaction) represents a reliable method to access structurally complex and bioactive molecules. The Heck–Matsuda arylation can be performed under aerobic conditions without requiring expensive and toxic phosphine ligands. Besides, these Heck arylation are much easier to carry out than conventional protocols. The first example of arenediazonium salts as arylating agents of olefins catalyzed by palladium was described by Tsutomu Matsuda in 1977. In spite of the many advantages and the long-term existence of the Heck–Matsuda (HM) reaction, its enantioselective version constitutes a considerable challenge due to the incompatibility of the phosphine ligands often used in the conventional Heck reactions with the arenediazonium salts.

Results and discussion

Herein, we describe the first protocol to perform an asymmetric version of the Heck–Matsuda reaction using chiral, nonracemic, bisoxazoline ligands (Fig. 1). The results presented might open the door for the next stage of development of the Heck–Matsuda reaction and its consolidation as a robust, reliable and broad scope synthetic method. The protocols reported in this work are very mild, fast and do not use any air-sensitive phosphines as chiral ligands or any anhydrous solvents.

We started our investigation using the symmetric and nonactivated olefin and the m-CF₃-substituted arenediazonium salt 2a as a model reaction to optimize conditions for asymmetric induction (Table 1). The Heck–Matsuda arylation of 1 using our previously reported procedure (Pd(OAc)₂, excess of arenediazonium salt in methanol at 60 °C) gave the desired product 3a in 93% yield after 5 h. Prompted by the excellent result obtained with olefin 1, we decided to employ the same protocol for our initial studies of the asymmetric version of the HM arylation using the chiral bisoxazoline 1 (Fig. 1). Under these conditions, the product 3a was obtained.
in a moderate 53% yield with a modest enantiomeric excess of 24% after 5 h (Table 1, entry 1). Changing the solvent to CH₂CN, PhCN, or dimethylcarbonate gave the corresponding Heck adduct only in trace amounts. PdCl₂(MeCN)₂ was also found to be a viable catalyst for the HM arylation of olefin 1. However, considering that different mechanisms (cationic, neutral and neutral pentacoordinate) might be operating and potentially eroding the enantioselectivity of the reaction in this case, we decided to use silver salts as halide scavengers.⁹ Therefore, when using PdCl₂(MeCN)₂ as catalyst we also added 1 equiv of Ag₂CO₃ to the reaction in order to remove chloride ions and establish the cationic pathway. We were delighted to find out that using bisoxazoline ⁷ that the increase in ee is probably due to the greater stability of the expected palladium complex as a five-membered chelate.¹⁰

Since only catalytic amounts of silver salt would be theoretically necessary, the amount of Ag₂CO₃ was reduced to 10 mol %. Interestingly, under this condition, we observed a sluggish reaction and a decrease in the ee’s to the extent of affording a roughly racemic product. On the other hand, an increase in the amount of Ag₂CO₃ (2 equiv) had a striking effect on the reaction time and a slight increase in yield. After 45 min, the product was obtained in 81% yield and 54% ee (Table 1, entry 2). In an attempt to understand the role of the silver salts, we carried out the arylation with catalytic Ag₂CO₃/Zn(OTf)₂. Surprisingly, we observed a further decrease in reaction time (20 min) while maintaining the good yield and moderate ee (Table 1, entry 3). Although the role of the Zn(OTf)₂ is not clear, we speculate that this Lewis acid might be operating and potentially eroding the enantioselectivity, affecting basically yields and reaction times (Table 1, entries 7–10 and 12). We then decided to evaluate other commercial bisoxazolines. Thus, bisoxazoline II was replaced by bisoxazolines I and III in the presence of Zn(OTf)₂ (Table 1, entries 7–9). The Heck products were obtained in good yields (75% and 81% respectively). However, in spite of the supposedly greater coordinating power of these ligands only racemic products were obtained. We then focused our attention on the role of the base considering that higher enantioselectivities were obtained in the presence of CO₂Me/F₃C⁺ (Table 1, entries 2–4). Gratifyingly, the use of 2,6-di-tert-butyl-4-methylpyridine (DTBMP) as base, furnished the Heck product in 83% yield in a very good ee of 84% after only 20 min (Table 1, entry 13).⁷ Surprisingly, NaOAc as base had a detrimental effect on the reaction providing a complex and inseparable mixture of products (Table 1, entry 14).²⁴ With optimized conditions in hand, an investigation of the scope of the enantioselective Heck–Matsuda reaction was initiated. As outlined in Table 2, we have found that a broad range of arenediazonium salts can be enantioselectively coupled to olefin 1. Both electron deficient and electron rich diazonium salts can be employed providing the Heck adducts in good to excellent yields (63% up to 96% yields) and good enantioselectivities (60% up to 84% ee) in less than an hour.¹¹ Interestingly, higher levels of enantioselectivity were obtained using electron deficient diazonium salts. In a few cases it was not possible to chromatographically separate the enantiomers. Therefore, in these cases we performed the measurement of the optical rotation of each product as an evidence of the asymmetric induction in the reaction (Table 1, entry 3, Table 2).

Increasing the olefin ring size from five to six-membered resulted in a decrease in the enantioselectivity of the arylation reaction (5 in Scheme 1). We rationalized this lower enantioselectivity as a consequence of the increasing conformational freedom of the six-membered olefin system when compared to the five-membered
Table 2
Enantioselective HM arylation of olefin 1 varying the arenediazonium salt

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>3a-k</td>
<td>96%</td>
<td>(84% ee)</td>
</tr>
<tr>
<td>b</td>
<td>3b</td>
<td>76%</td>
<td>(74% ee)</td>
</tr>
<tr>
<td>c</td>
<td>3c</td>
<td>83%</td>
<td>(84% ee)</td>
</tr>
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<td>d</td>
<td>3d</td>
<td>87%</td>
<td>(74% ee)</td>
</tr>
<tr>
<td>e</td>
<td>3e</td>
<td>63%</td>
<td>(76% ee)</td>
</tr>
<tr>
<td>f</td>
<td>3f</td>
<td>74%</td>
<td>(72% ee)</td>
</tr>
<tr>
<td>g</td>
<td>3g</td>
<td>76%</td>
<td>(60% ee)</td>
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<tr>
<td>h</td>
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<td>91%</td>
<td>(70% ee)</td>
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<tr>
<td>i</td>
<td>3i</td>
<td>96% (60% ee)</td>
<td></td>
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<tr>
<td>j</td>
<td>3j</td>
<td>83%</td>
<td>(90% ee)</td>
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<tr>
<td>k</td>
<td>3k</td>
<td>85%</td>
<td>(60% ee)</td>
</tr>
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Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.079.

References and notes

5. Most phosphines are incompatible with arenediazonium salts due to single-electron transfer processes. See Ref.2a for details.
