<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>A general method for asymmetric arylation and vinylation of silyl ketene acetals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author(s)</strong></td>
<td>Yang, Junfeng; Zhou, Jianrong (Steve)</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>2014</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10220/44886">http://hdl.handle.net/10220/44886</a></td>
</tr>
<tr>
<td><strong>Rights</strong></td>
<td>© 2014 the Partner Organisations. This is the author created version of a work that has been peer reviewed and accepted for publication by Organic Chemistry Frontiers, the Partner Organisations. It incorporates referee’s comments but changes resulting from the publishing process, such as copyediting, structural formatting, may not be reflected in this document. The published version is available at: [<a href="http://dx.doi.org/10.1039/C4QO00027G">http://dx.doi.org/10.1039/C4QO00027G</a>].</td>
</tr>
</tbody>
</table>
A General Method for Asymmetric Arylation and Vinylation of Silyl Ketene Acetals

Junfeng Yang and Jianrong (Steve) Zhou*

Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX
DOI: 10.1039/b000000x

A new biarylmonophosphine was developed for highly asymmetric arylation and vinylation of silyl enolates of acyclic esters with generality. The new stereocenters α to ester groups were formed in high enantiomeric excess. The method was applied to asymmetric synthesis of Profen drugs in a gram scale.

In method development of asymmetric α-arylation of carbonyl compounds, the main driving force is the need to prepare enantiopure Profens. Profens are a family of nonsteroidal anti-inflammatory drugs, including over-the-counter painkillers such as Naproxen, Profen, and Ketoprofen. They all contain the core structure of α-arylpropionic acids having tertiary stereocenters at α positions. Profen enantiomers are known to possess significantly different pharmacological profiles. The (S) isomers are more biologically active than (R) forms. Consequently, Naproxen is sold solely in (S) form. Today, to access α-arylcarboxylic acids and derivatives, resolution and asymmetric C-C couplings are common. Among them, direct asymmetric coupling between aryl electrophiles and enolates is one of the most efficient ways to access these compounds. In the past decade, a number of α-arylations of enolates have been developed to form quaternary centers in high ee (Fig 1a). The enolates were in situ generated from strong bases and carbonyl compounds including lactones, ketones, aldehydes and oxindoles. The use of strong bases prevented these methods from the construction of tertiary α-stereocenters, due to facile racemization of those products under basic conditions. Recently, we realized α-arylation of enolates in high ee which produced tertiary α-stereocenters. To prevent product racemization, silicon and tin enolates of esters, lactones and ketones were used (Fig 1b). Other related metal-catalyzed methods were also reported. Examples include Cu-catalyzed coupling of diarylodonium salts and soft enolates and Ni-catalyzed coupling of α-bromoesters and α-metal reagents (Fig 1c). In our previously reported α-arylation of esters using chiral ligand L4, most aryl triflates carrying para-groups gave <90% ee. For example, the coupling of p-anisyl triflate and t-butyl propionate ended in 85% ee and the reaction stopped after partial conversion.

We decided to use the model coupling between p-anisyl triflate and a trimethylsilyl enolate derived from t-butyl propionate to seek a more stereoselective catalyst (Fig 2). Based on our past experience in arylation of ketones and lactones, we hypothesized that the modification of O-benzyl side arm of ligand L4 may help. Indeed monophosphines L5 and L7 carrying m-CF3-benzyl groups led to 93% and 94% ee, respectively. Most other modification on the benzyl group led to inferior selectivity. In comparison, similar biarylphosphines on a 1,1'-binaphthyl backbone afforded only 30-64% ee.

Fig 1 Asymmetric C-C couplings to prepare α-arylesters and -aryllactones (structure of L4, see Fig 2).

Fig 2 Performance of chiral biarylphosphines in asymmetric coupling.
The choice of other reaction parameters was also crucial to good ee. (TMEDA)PdMe₂ was the optimal Pd source and Pd(OAc)₂ also gave good yield. LiOAc was essential to facilitate efficient enolate transfer. The ZnF₂ additive (0.2 equiv) can further accelerate the process. In terms of choice of solvents, good yield can also be obtained in toluene, benzene, α-xylene and diethyl ether. In PhCF₃, the model reaction of anisyl triflate was much slower and stopped after a partial conversion.

The Pd/L7 catalyst was successfully applied to many structurally diverse aryl triflates (Fig 3a). In almost all cases ligand L7 was more stereoselective than ligand L4. Both electron-donating and electron-withdrawing groups can be present on the aryl rings. For an electron-neutral or electron-rich ArOTf, better ee was obtained in toluene than in PhCF₃. For an electron-poor ArOTf, however PhCF₃ was a better solvent. Notable, several alkyl triflates also coupled well in toluene solvent. Silyl ketene acetals of n-butylate and valerate also coupled well (Fig 3b).

The Pd/L7 catalyst was successfully applied to asymmetric synthesis of some Profens including Fenoprofen, Flurbiprofen, Ketoprofen and Naproxen (Fig 4). In most cases, the coupling proceeded smoothly in >90% ee. The t-butylic esters of products can be easily hydrolyzed to release Profens using trifluoroacetic acid. After one crystallization the ee of synthetic Flurbiprofen was improved to 96% (84% yield) and after recrystallization, to 99%. The absolute configuration of synthetic Naproxen was determined to be (2S) by comparison with the reported optical rotation.

In summary, we report herein a general Pd catalyst for asymmetric arylation and vinylnation of ester enolates that formed tertiary carbon centers. The enantioselectivity was uniformly high as compared to our previous report in 2011.† The method allows a quick access to many Profen analogues in >90% ee with a general scope. In our recent asymmetric arylation of cyclic ketones and lactones, weak CH–O hydrogen bonding was found to be responsible for asymmetric induction and the C–C reductive elimination was the stereo-determining step.† In the arylation of silyl enolates of acrylic esters, however it is probably transmetalation that dictates the stereochemical outcome, since (E) and (Z) isomers of a silyl ketene acetate gave significantly different ee values during arylation.

We thank the Singapore National Research Foundation (NRF–RF2008–10) and Nanyang Technological University for financial support. We thank Johnson Matthey for a gift of palladium salts.

**Notes and references**

Division of Chemistry and Biological Chemistry

School of Physical and Mathematical Sciences

Nanyang Technological University, 21 Nanyang Link, Singapore 637371

† Electronic Supplementary Information (ESI) available: Experimental procedures for asymmetric coupling and characterization of new compounds. See DOI: 10.1039/b000000x/


A general palladium catalyst was developed for asymmetric coupling of silyl ketene acetals with a wide range of aryl and vinyl triflates, which was applied to several Profen synthesis.