A General Method for Asymmetric Arylation and Vinylation of Silyl Ketene Acetals

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ARTICLE TYPE

A General Method for Asymmetric Arylation and Vinylation of Silyl Ketene Acetals

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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 Ibuprofen, Naproxen, and Ketoprofen. They all contain the core structure of α-arylpropionic acids having tertiary stereocenters at α positions.[1] 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[2] and asymmetric C-C couplings[3] 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).[4] The enolates were *in situ* generated from strong bases and carbonyl compounds including lactones,[5] ketones,[6] aldehydes[7] and oxindoles.[8] 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,[9] lactones[10] and ketones[11] were used (Fig 1b). Other related metal-catalyzed methods were also reported. Examples include Cu-catalyzed coupling of diaryliodonium salts and soft enolates[12] and Ni-catalyzed coupling of α-bromoesters and aryl-metal reagents (Fig 1c).[13]

In our previously reported α-arylation of esters using chiral ligand **L4**, most aryl triflates carrying *para*-groups gave <90% *ee*.[9] 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[11] and lactones,[10] we hypothesized that the modification of *O*-benzyl side arm of ligand **L4** may help. Indeed monophosphines **L5** and **L7** carrying *m*-CF_3-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*.

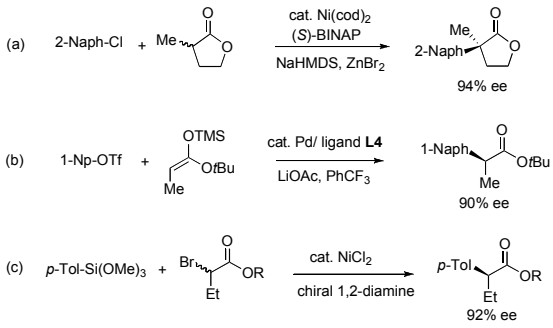

Fig 1 Asymmetric C-C couplings to prepare α−arylesters and −aryllactones (structure of L4, see Fig 2).

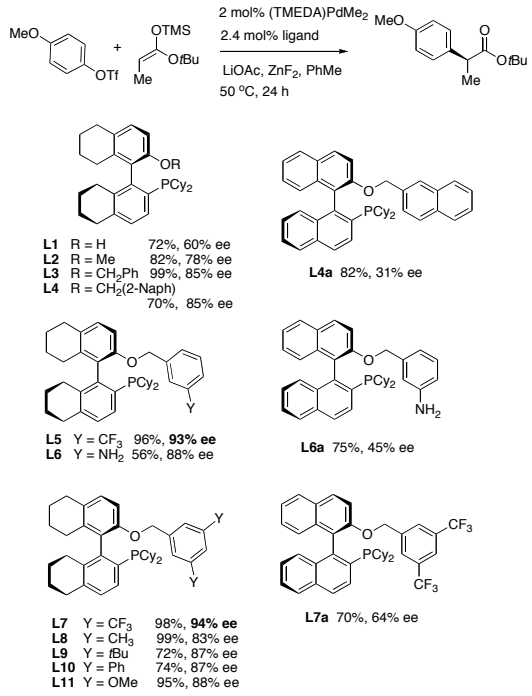

Fig 2 Performance of chiral biarylphosphines in asymmetric coupling.

The choice of other reaction parameters was also crucial to good *ee*. (TMEDA)$PdMe_2$ was the optimal Pd source and $Pd(OAc)_2$ also gave good yield. LiOAc was essential to facilitate efficient enolate transfer. The ZnF_2 additive (0.2 equiv) can further accelerate the process. In terms of choice of solvents, good yield can also be obtained in toluene, benzene, *o*-xylene and diethyl ether. In $PhCF_3$, 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 of cases ligand **L7** was more stereoselective than ligand **L4**.[9] 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 $PhCF_3$. For an electron-poor ArOTf, however $PhCF_3$ was a better solvent. Notably, several alkenyl 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*.[14] The *t*-butyl 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 (2*S*) by comparison with the reported optical rotation.[15]

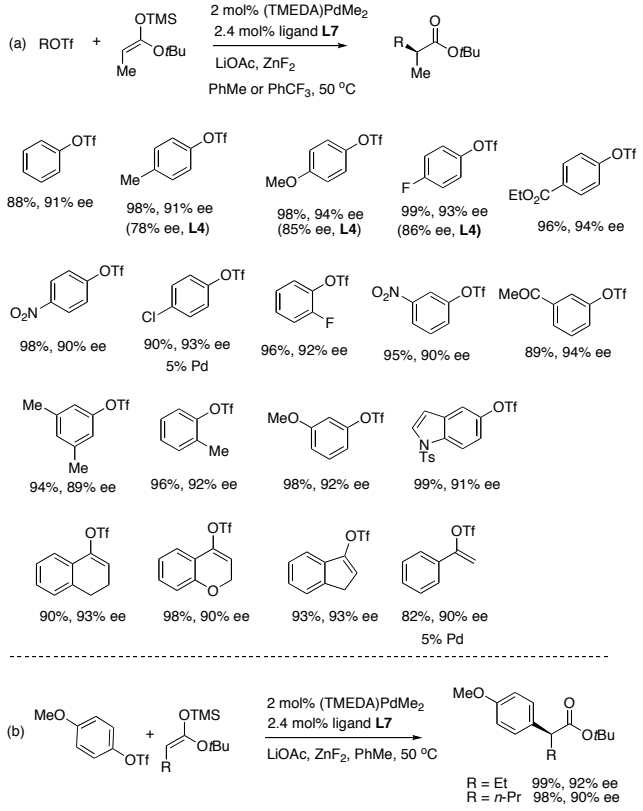

Fig 3 Examples of aryl and vinyl triflates in asymmetric coupling of enolates.

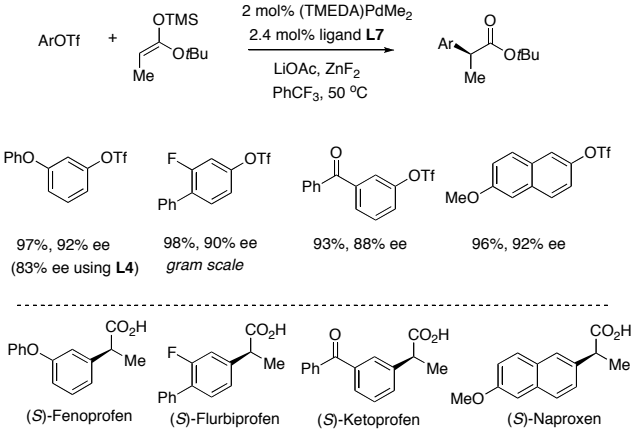

Fig 4 Asymmetric synthesis of Profen esters.

In summary, we report herein a general Pd catalyst for asymmetric arylation and vinylation of ester enolates that formed tertiary carbon centers. The enantioselectivity was uniformly high as compared to our previous report in 2011.[9] The method allows a quick access to many Profen analogues in >90% *ee* with a general scope. In our recent asymmetric arylations 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.[10-11] In the arylation of silyl enolates of acyclic esters, however it is probably transmetalation that dictates the stereochemical outcome, since (*E*) and (*Z*) isomers of a silyl ketene acetal gave significantly different *ee* values during arylation.[9]

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Notes and references

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

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A general method is described for asymmetric coupling of ester enolates and both aryl and vinyl triflates, which was useful to asymmetric Profen synthesis.