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An Enantioselective, Intermolecular α-Arylation of Ester Enolates To Form Tertiary Stereocenters

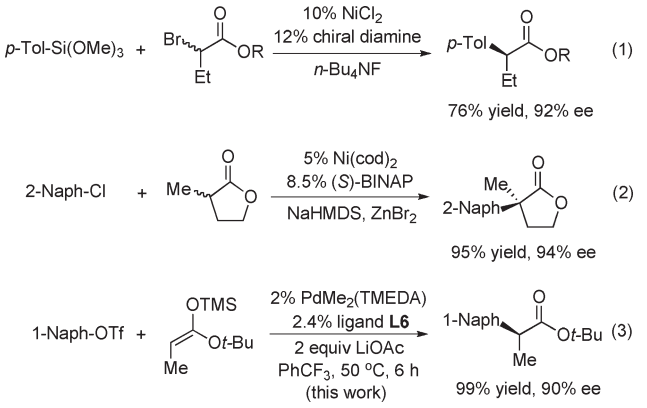
Zhiyan Huang, Zheng Liu, and Jianrong (Steve) Zhou*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: In transition-metal catalyzed, asymmetric α-arylation of carbonyl compounds, formation of tertiary centers with high enantioselectivity is a longstanding problem, due to easy enolization of the monoarylation products. Herein, we report such examples using a palladium catalyst supported by a new, (*R*)-H_8-BINOL-derived monophosphine. Silyl ketene acetals, together with a weakly basic activator, were used as equivalents of ester anions, and they reacted smoothly with aryl triflates in excellent enantiomeric excess (ee). The usefulness of the reaction was demonstrated in a gram-scale synthesis of (*S*)-Naproxen in 92% ee.

Chiral α-arylalkanoic acids and derivatives are core structures in many drug molecules. For example, the Profen family of nonsteroidal anti-inflammatory drugs are all α-arylpropionic acids, including blockbusters such as Ibuprofen, Naproxen, and Ketoprofen.[1] Their enantiomers are known to display substantially different pharmacological profiles and Naproxen is sold in its optically pure (*S*)-form. To achieve convergent and efficient synthesis, aryl groups are best introduced with concomitant establishment of chirality. However, asymmetric α-arylation of esters using either aryl-metal reagents or aryl electrophiles has met only with limited success. One example was reported by Fu et al. recently, in which arylsilanes were used as equivalent of "aryl-metal" reagents.[2] They underwent Ni-catalyzed coupling with racemic α-bromoester to give products containing tertiary centers in high enantiomeric excess (ee) (eq 1). A more straightforward disconnection would involve C−C bond formation between aryl halides/sulfonates and enolate anions.[3] Successful examples of this kind with excellent ee were surprisingly scarce. In the work by Buchwald and co-workers, aryl chlorides were used to couple with enolates generated in situ from γ-butyrolactone and a strong base (eq 2).[4] Although a high level of ee was achieved, the method was limited to the formation of quaternary stereocenters. In fact, all of metal-catalyzed, enantioselective arylations of carbonyl compounds (including ketones,[5] aldehydes,[6] oxindoles,[7] and α-methylacetoacetates[8]) suffered from the same limitation.[9] The challenge to produce tertiary centers lies in that the monoarylation products contain more acidic α-hydrogens than the starting material, and they can be readily deprotonated under basic conditions. The deprotonation can eventually lead to racemization and, in some cases, double arylation. In this communication, we report an efficient α-arylation of ester anions to produce tertiary centers with high ee.



Silyl ketene acetals in combination with activators have been studied as equivalent of ester anions in diastereoselective arylations.[10] We reason that if the activators are not basic enough to deprotonate α-arylesters, asymmetric arylation to form tertiary centers is plausible with catalyst control of stereochemistry. Indeed in our model arylation of 1-naphthyl triflate (eq 3), the use of LiOAc activator allowed efficient coupling of an *O*-trimethylsilyl ketene acetal, which was derived from *tert*-butyl propionate. In presence of a palladium catalyst supported by phosphine ligand **L6**, 90% ee was realized. The reaction was devoid of racemization and double arylation and the ee of the monoarylation product remained constant during the course of the reaction. Other activators such as NaOAc, KOAc, CsOAc and CsF were much less effective (for details, see Supporting Information).

Among some common palladium complexes, $PdMe_2$(TMEDA) turned out to be superior in the model reaction. When it was replaced by $Pd(dba)_2$, the coupling became slower, probably due to competitive binding of dba to the active catalyst LPd(0). Inclusion of 0.2 equiv of ZnF_2 as coactivator can bring back the activity and afforded the coupling product in 99% yield and 92% ee after 24 h at 50 °C (see Supporting Information).

From our extensive screening of chiral ligands, a series of (*R*)-H_8-BINOL-derived monophosphines **L1**−**6** emerged to be most promising (Table 1). Finetuning of the ligand *O*-alkyl R′ group revealed that 2-naphthylmethyl in **L6** was optimal in terms of both reactivity and stereoinduction (entry 6). Similar (*R*)-BINOL-derived ligands **L7** and **L8** were not as selective

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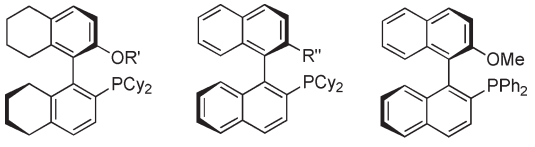
Table 1. Effect of Chiral Phosphine Ligands (Same Conditions as in eq 3)

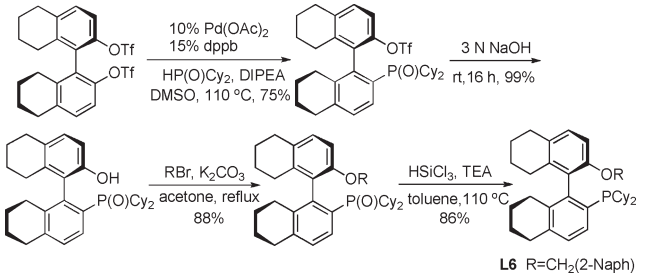


L1 R'=H
L2 Me
L3 *i*-Pr
L4 Bn
L5 CH_2(1-Naph)
L6 CH_2(2-Naph)

L7 R''=OBn
L8 OCH_2(2-Naph)
L9 NMe_2 (*R*)-KenPhos

L10 (*R*)-MOP

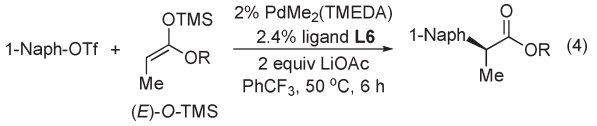
entry	ligand	yield (%)	ee (%)
1	**L1**	55	68
2	**L2**	63	81
3	**L3**	37	72
4	**L4**	71	86
5	**L5**	40	85
6	**L6**	99	90
7	**L7**	76	67
8	**L8**	46	70
9	**L9**	62	12
10	**L10**	2	26



L6 R=CH_2(2-Naph)

Figure 1. Synthesis of ligand **L6**.

Table 2. Effect of Silyl Ketene Acetals



entry	R	yield (%)	ee (%)
1	Me	99	5
2	Et	99	5
3	Cy	99	67
4	*t*-Bu	99	90
5	2-Naph	99	52
6	*t*-Bu[a]	95	50

[a] (*Z*)-*O*-TMS ketene acetal.

(entries 7–8). KenPhos **L9** containing an NMe_2 group and MOP **L10** were much less satisfactory (entries 9–10). All the ligands can be easily assembled and a typical synthesis of **L6** is shown in Figure 1. Ligands **L1**–**6** are octahydro analogues of BINOL-derived ligands used in Buchwald's previous study.[5c]

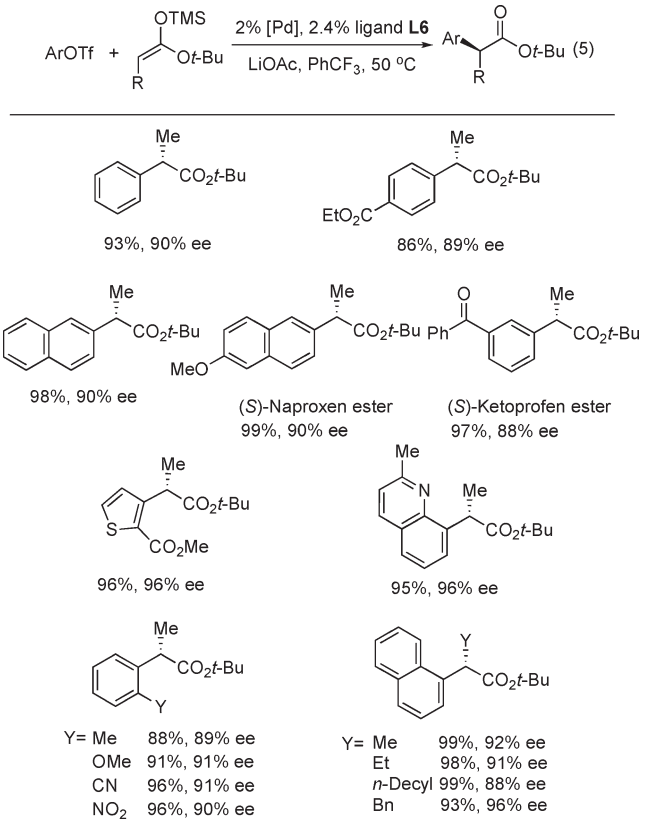
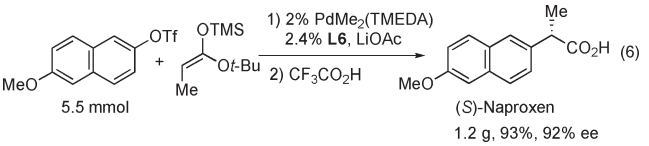


Figure 2. Substrate scope.



Notably, the structure of silyl ketene acteals has a large influence on the outcome of the asymmetric coupling (Table 2). First, the size of R groups in the (*E*)-*O*-TMS ketene acetals affects the ee significantly (entries 1–5). For instance, <10% ee was observed if R was methyl or ethyl (entries 1–2), while 90% ee was achieved when R was *t*-butyl (entry 4). Second, the geometry of the *O*-TMS ketene acetals is very important, to our surprise. The (*E*)-isomer afforded 90% ee, while the (*Z*)-isomer only gave modest 50% ee (entry 4 versus 6). This result indicates that no lithium enolate is produced from the silyl ketene acetal and LiOAc, since geometric isomers of the former can quickly equilibrate. The result also contradicts with common belief that after transmetalation, enantiomeric (*C*)-bound Pd-enolates can undergo fast equilibration via the (*O*)-bound form before reductive elimination.[11] Thus, under our condition, equilibration of (*C*)-bound enolates is slower than reductive elimination. Third, the corresponding *C*-trimethylsilyl enolate did not react at all. Fourth, the corresponding (*E*)-*O*-*t*-butyldimethylsilyl ketene acetal was completely unreactive.

The Pd/**L6** catalyst can be applied to couplings of various aryl triflates, as shown in Figure 2. In all cases, full conversion was achieved with only 2 mol % $PdMe_2$(TMEDA) or $Pd(dba)_2$ and 2.4 mol % ligand **L6**. In some cases, inclusion of 0.2 equiv of ZnF_2 additive was beneficial to reaction rates. Both electron-donating and -withdrawing groups can be present. These groups can be

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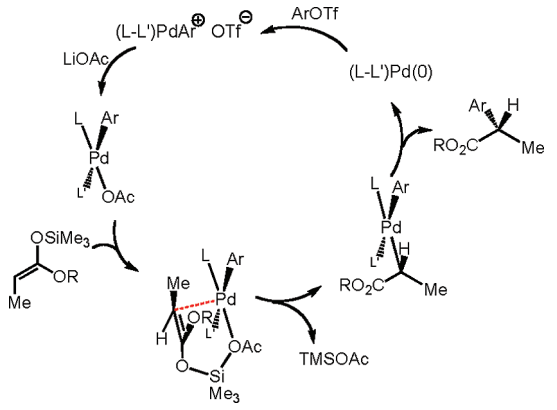

Figure 3. A proposed catalytic cycle.

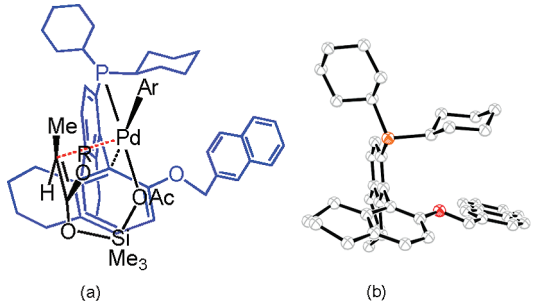

Figure 4. (a) Transmetalation assembly with ligand **L6** colored in blue and (b) ORTEP of ligand **L6**.

located on not only *para* and *meta* positions of the aromatic rings, but also the more hindered *ortho* sites. The condition is compatible with sensitive functional groups such as nitro, nitrile, ester and ketone. Two examples of heteroaryl triflates are included to illustrate the generality of the method. Moreover, three more examples of silyl ketene acetals with α-alkyl substituents can couple efficiently with high ee.[12] It is worth pointing out that all of the *O*-TMS ketene acetals (except Y = Bn) can be easily prepared in good yield and excellent (*E*):(*Z*) ratio (99:1). Following a reported procedure, *t*-butyl esters were first treated with LDA at 0 °C in a mixed solvent of cyclohexane/cyclopentyl methyl ether, followed by TMSCl quenching.[13]

The reaction can be easily scaled up to produce 1.2 g of (*S*)-Naproxen, after acidic hydrolysis of the ester (eq 6). The product ee can be improved from 92% to 99% after a simple crystallization. The configuration of the new stereocenter was assigned to be (*S*) by comparison with reported optical rotation.[14]

We propose a catalytic cycle (Figure 3) that starts from oxidative addition of ArOTf to form cationic LPdAr species. Binding of acetate anion facilitates the transfer (transmetalation) of the enolate from silicon to palladium via an acetate-bridged structure. Subsequent C−C reductive elimination directly leads to the arylation product. Equilibration of the (*C*)-enolate to its epimer via the (*O*)-enolate intermediate is probably much slower than reductive elimination in this case.

To account for the formation of (*S*)-products, we propose in Figure 4a that ligand **L6** is bound to Pd via both phosphorus (L) and *ipso* carbon of the bottom ring (L′). This kind of Pd−arene interaction has been reported previously in (MOP)Pd complexes.[15] Judged from the X-ray structure of **L6** shown in Figure 4b, the right side of the ligand is more hindered due to specific orientation of the *P*-cyclohexyl group and/or conformational flexibility of the *O*-CH_2Ar' group. Thus, the enolate is expected to transfer to Pd from the left side. Furthermore, (*E*)- and (*Z*)-silyl enolates were shown to give very different ee in the product, indicating that a cyclic, closed transition state is operating during transmetalation instead of an open one. In the acetate-bridged transition state, both (*E*)-geometry and bulky OR group of the silyl enolate ensure enolate delivery from its *Re* face. Transfer from the *Si* face will require the OR and methyl groups of the enolate to point toward the bottom ring of **L6**, and result in unfavorable steric repulsion. A similar analysis can be used to understand why (*Z*)-ketene acetals gave low ee. Transfer from either face of the (*Z*)-ketene acetals will always place one of OR and methyl groups close to the bottom ring.

In summary, we have achieved the first examples of α-arylation of esters to form tertiary centers with high ee. The combination of silyl ketene acetals and a mild activator made it possible to avoid racemization and/or double arylation of the monoarylation products. The method is applicable to a gram-scale synthesis of (*S*)-Naproxen in 92% ee. Extension of the new method to asymmetric coupling of ketone enolates is ongoing.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures for the synthesis of reactants and chiral phosphine ligands, asymmetric coupling and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
jrzhou@ntu.edu.sg

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