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# Highly Regio-, Diastereo-, and Enantioselective Pd-Catalyzed Allylic Alkylation of Acyclic Ketone Enolates with Monosubstituted Allyl Substrates

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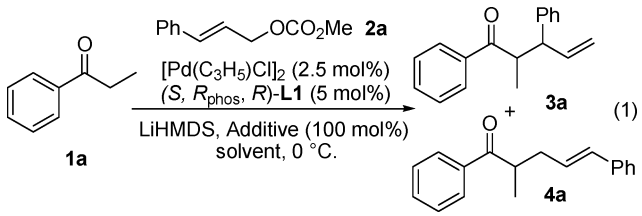
Palladium-catalyzed asymmetric allylic alkylation (AAA) has become one of the most powerful tools for constructing chiral centers via carbon−carbon bond forming reactions.[1] However, regioselectivity is still not fully resolved when monosubstituted allyl substrates are used,[1−4] and the carbon nucleophiles are restricted mainly to "soft", stabilized carbanions.[1] In the past several years, great progress has been made in Pd-catalyzed AAA reactions in the control of both regio- and enantioselectivities involving monosubstituted allyl substrates[2−4] and nonstabilized ketone enolates.[3a,5−7] Procedures have also been developed for installment of two chiral centers through combination of allyl substrates and nucleophiles, such as in Pd- and Mo-catalyzed reactions of azalactone with cyclohexyl acetate, PhCH═CHCH(OAc)$_2$,[8a] and ArCH═CHCH$_2$X,[8b] in Ir-catalyzed reactions of glycine derivatives with monoallyl substrates,[9] or Pd-catalyzed reactions of cyclohexanones with 1,3-disubstituted allyl acetate,[5b,g] all showing good to excellent regio-, diastereo-, and enantioselectivities. High regio- and diastereoselectivities were also achieved in the Rh-catalyzed reaction of acyclic α-alkoxy ketones with branched allyl carbonates.[10] However, chiral allyl carbonates must be used in order to obtain enantioenriched products. To the best of our knowledge, a method to generate two chiral centers by transition-metal-catalyzed asymmetric reactions of simple ketone enolates and monosubstituted allyl substrates is still lacking. Recently, we have developed a series of chiral ferrocene ligands, which have been utilized successfully in Pd-catalyzed regio- and enantioselective AAA.[3] Subsequent extension to include acyclic ketone enolates as the nucleophiles was achieved by us and others.[5h,6b,7] In this paper, we describe a Pd-catalyzed AAA of monosubstituted allyl substrates with simple acyclic ketone enolates, while establishing two chiral centers with high regio-, diastereo-, and enantioselectivity.




Our initial investigation in the reaction of propiophenone **1a** with cinnamyl methyl carbonate **2a** using LiHMDS as base in the presence of 2.5 mol % of [Pd(C$_3$H$_5$)Cl]$_2$ and 5 mol % of (*S*,*R*$_{phos}$,*R*)-**L1** failed. However, since **4a** was obtained in 87% yield when 1 equiv of CuI was added,[10] the effect of additives was assessed (eq 1, Table 1). Some simple salts appear to exert dramatic effect on the regioselectivity of the reaction. For example, **4a** was only the product using CuI as additive, **3a** and **4a** were produced in a ratio of 84:16 in the presence of CuBr (entry 1 vs entry 2), and the ratio increased to about 95:5 when CuCl or LiCl was used (entries 3 and 4). The reaction was arrested on the addition of LiI (entry 5), yet a combination of CuI and LiCl (entry 6) or CuCl and LiI (entry 7) allowed the reaction to proceed smoothly. In these cases, however, only linear product **4a** was observed.

***Table 1.*** Effects of Additives and Solvents on the Pd-Catalyzed Reaction of **1a** and **2a**[a]

| entry | additive | solvent | yield%[b] | **3a**:**4a**[c] | *anti*:*syn*[c] **3a** | *anti*-**3a** ee%[d] |
|---|---|---|---|---|---|---|
| 1 | CuI | THF | 87 | 0:100 | − | − |
| 2 | CuBr | THF | 84 | 84:16 | 2:1 | ND[g] |
| 3 | CuCl | THF | 91 | 94:6 | 2:1 | ND |
| 4 | LiCl | THF | 86 | 95:5 | 2:1 | ND |
| 5 | LiI | THF | NR | − | − | − |
| 6 | CuI[e] | THF | 80 | 0:100 | − | − |
| 7 | CuCl[f] | THF | 79 | 0:100 | − | − |
| 8 | LiCl | Et$_2$O | 90 | 84:16 | 2:1 | ND |
| 9 | LiCl | toluene | 96 | 85:15 | 2:1 | 98 |
| 10 | LiCl | $^t$BuOMe | 96 | >98:2 | 2:1 | ND |
| 11 | LiCl | dioxane | 96 | 85:15 | 4:1 | 96 |
| 12 | LiCl | DME | 90 | 95:5 | 6:1 | 98 |

[a] Molar ratio of **1a**/[Pd(C$_3$H$_5$)Cl]$_2$/(*S*,*R*$_{phos}$,*R*)-**L1**/LiHMDS/**2a**/additive = 100/2.5/5/100/100/110/100. [b] Isolated yield by preparative TLC. [c] Determined by 300 MHz $^1$H NMR. [d] Determined by chiral HPLC. [e] 1 equiv of LiCl was added. [f] 1 equiv of LiI was added. [g] ND = not determined.

As shown in Table 1, good regioselectivity was achieved, but diastereomer ratios were quite low in several common solvents (entries 8−11), the best being DME, in which the dr increased to 6:1 (entry 12). Also in the case, both regio- and enantioselectivities are excellent. On comparing these results from Table 1, we conclude that the state of carbanion aggregation played an important role in the selectivities.[5g,11]

The influence of substituent on the oxazoline ring of the ligand was also investigated. Ligands **L1**−**L6**[3] (Figure 1) were all effective. Ligands **L1**−**L5** provided products **3a** and **4a** in a ratio of 93−98:7−2 and in the yields ranging from 90 to 97%, with the *anti*:*syn* ratio for **3a** being 6:1 and the ee for *anti*-**3a** being 96−98%. Interestingly, ligand **L6**, which does not have an additional substituent in the oxazoline ring, gave the best diastereoselectivity (7:1), while the **3a**:**4a** ratio was >98:2, and the ee for *anti*-**3a** was 98%. An increase in the dr ratio to 9:1 was observed when the reaction was conducted at −5 °C.

The scope of the reaction was examined (eq 2). The results are compiled in Table 2. In general, the reaction proceeded smoothly to afford allylation products in high yields. Excellent regio- and enantioselectivities were realized for all substrates, with the ratio of **3**:**4** being >98:2, while the ee value was 92−99%. The reactions also occurred with good to excellent diastereoselectivity, with a ratio of *anti*:*syn* for products **3** between 5 and 21:1. An electron-withdrawing group on the phenyl ring of the carbonate does not seem to affect the selectivity (entries 1 and 3). Employing substrates bearing a more electron-rich aromatic ring led to slightly lower diastereo- and enantiomeric excesses (entries 5 and 9). Replacing the phenyl group with a naphthyl group in either the ketone or the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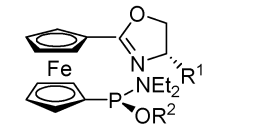



$R^2$ = (*R*)-1,1'-bi-2-naphthol

(*S*, $R_{phos}$, *R*)-**L1**. $R^1$ = $^i$Pr
(*S*, $R_{phos}$, *R*)-**L2**. $R^1$ = $^t$Bu
(*S*, $R_{phos}$, *R*)-**L3**. $R^1$ = Ph
(*S*, $R_{phos}$, *R*)-**L4**. $R^1$ = Bn
(*S*, $R_{phos}$, *R*)-**L5**. $R^1$ = Me
($R_{phos}$, *R*)-**L6**. $R^1$ = H

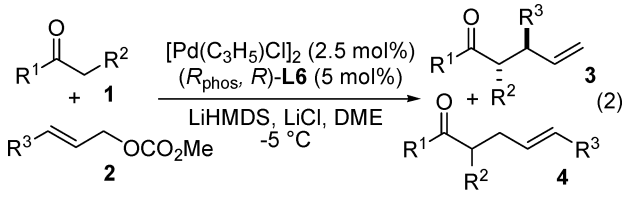
***Figure 1.*** Ferrocene-based ligands **L1**−**L6**.

***Table 2.*** Reaction Scope: Variation of Electrophile and Nucleophile[a]

| entry | Substrate 1 | Substrate 2 | yield%[b] | 3:4 | *anti*:*syn*[c] 3 | *anti*-3 ee%[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 83 | 98:2 | 9:1 | 98 |
| 2 | **1a** | **2b** | 90 | >98:2 | 8:1 | 98 |
| 3 | **1a** | **2c** | 80 | >98:2 | 9:1 | 96 |
| 4 | **1a** | **2d** | 85 | >98:2 | 10:1 | 99 |
| 5 | **1a** | **2e** | 73 | >98:2 | 7:1 | 92 |
| 6 | **1a** | **2f** | 83 | >98:2 | 20:1 | 99 |
| 7 | **1b** | **2a** | 88 | >98:2 | 7:1 | 92 |
| 8 | **1c** | **2a** | 85 | >98:2 | 8:1 | 98 |
| 9 | **1d** | **2a** | 82 | >98:2 | 7:1 | 97 |
| 10 | **1e** | **2a** | 89 | >98:2 | 21:1 | 93 |
| 11[e] | **1f** | **2e** | 72 | >98:2 | 5:1 | 99 |

[a] Molar ratio of **1**/[Pd($C_3H_5$)Cl]$_2$/($R_{phos}$,*R*)-**L6**/LiHMDS/LiCl = 100/2.5/5/100/100/110. [b] Isolated yield by preparative TLC. [c] Determined by 300 MHz $^1$H NMR. [d] Determined by chiral HPLC. [e] Molar ratio of **1**/[Pd($C_3H_5$)Cl]$_2$/($R_{phos}$,*R*)-**L6**/LiHMDS/LiCl = 100/5/10/120/200.

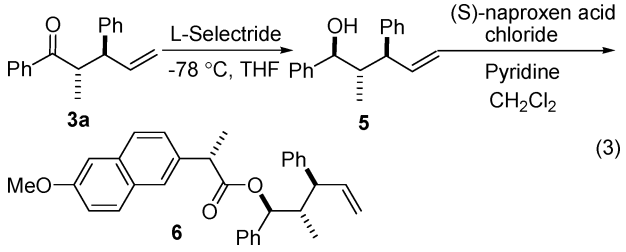
electrophile gave high diastereomeric excess (up to 21:1) (entries 6 and 10). Nonaromatic ketones may also be suitable substrates to give products in high ee, although our examples are limited (entry 11). The length of a normal alkyl chain in **1** did not affect the reaction (entries 7 and 8), but the reaction of phenyl isobutylketone gave inferior results. The reaction can be scaled up to gram scale. For example, reaction of 0.80 g of **1a** with 1.27 g of **2a** under the above condition gave 75% yield of **3a** in the same regio-, diastereo-, and enantioselectivities. It is interesting to note that the reaction led to lower selectivities when cinnamyl acetate was used. Lower yields from reactions with allyl- and alkyl-substituted allyl carbonates were also observed.




**1a**. $R^1$= Ph, $R^2$= Me; **2a**. $R^3$= Ph;
**1b**. $R^1$= Ph, $R^2$= Et; **2b**. $R^3$ = *p*-$FC_6H_4$;
**1c**. $R^1$= Ph, $R^2$= n-Pr; **2c**. $R^3$ = *p*-$MeC_6H_4$;
**1d**. $R^1$= *p*-$MeOC_6H_4$, $R^2$= Me; **2d**. $R^3$ = *m*-$BrC_6H_4$;
**1e**. $R^1$= 1-Naphthyl, $R^2$= Me **2e**. $R^3$ = *p*-$MeOC_6H_4$;
**1f**. $R^1$= cyclohexyl, $R^2$= Me **2f**. $R^3$ = 1-Naphthyl;

Although the diastereoisomers **3** could not be separated, pure alcohol **5** was isolated after L-Selectride reduction of **3a** stereospecifically. Reaction of **5** with (*S*)-naproxen acid chloride provided **6** (eq 3). Its X-ray diffraction analysis showed the absolute configuration of hydroxyl product **5** to be (*S*,*S*,*S*).

In summary, we have realized Pd-catalyzed AAA using acyclic ketones and monosubstituted allyl carbonates in the construction of two chiral centers in products with high regio-, diastereo-, and enantioselectivities. Ferrocenyloxazoline ligands are highly effective. In this work, we also found some interesting effects of additives




and solvents. Further investigations to extend the reaction scope and applications of this methodology in organic synthesis are in progress.

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**Supporting Information Available:** General procedure for allylic alkylation, spectral and HPLC data for **3a**−**3k**, and X-ray analysis data of **6** (cif file). This material is available free of charge via the Internet at http://pubs.acs.org.

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