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Enantioselective Construction of All-Carbon Quaternary Stereocenters Using Palladium-Catalyzed Asymmetric Allylic Alkylation of γ-Acetoxy-α,β-unsaturated Carbonyl Compounds

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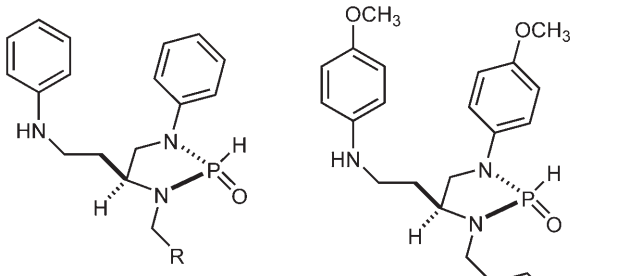
Abstract: We have successfully demonstrated that γ-acetoxy-α,β-unsaturated carbonyl compounds are useful starting materials for Pd-catalyzed asymmetric allylic alkylation to construct all-carbon quaternary stereocenters. With the use of 2–5 mol % of Pd catalyst and 4–10 mol % of P-chirogenic diaminophosphine oxides, asymmetric allylic alkylation of γ-acetoxy-α,β-unsaturated carbonyl compounds with various prochiral nucleophiles derived from cyclic β-keto esters proceeded in the presence of $Zn(OAc)_2$, providing the corresponding products with an all-carbon quaternary stereocenter in up to 95% ee.

Keywords: all-carbon quaternary stereocenter; asymmetric allylic alkylation; asymmetric catalysis; diaminophosphine oxide; palladium

The efficient creation of all-carbon quaternary centers is a formidable challenge in organic synthesis, due to steric repulsion during the C–C bond forming process. This challenge is magnified when the carbon center is stereogenic. The catalytic asymmetric C–C bond forming reaction is the most effective method for the synthesis of all-carbon quaternary stereocenters.[1] There are, however, few catalytic asymmetric processes available to construct such a congested chiral center with a synthetically useful level of enantioselection.[2] Pd-catalyzed asymmetric allylic alkylation (AAA) using prochiral nucleophiles is one of the most straightforward approaches toward this end. Limited success of this type reaction has been reported since the 1980 s.[3–6] We recently succeeded in the Pd-catalyzed asymmetric construction of all-carbon quaternary stereocenters using novel pentavalent chiral phosphorus ligands: P-chirogenic diaminophosphine oxides (DIAPHOXs) (Figure 1).[7] In this reaction system, pentavalent phosphorus compounds, the preligands, are activated *in situ* by *N,O*-bis(trimethylsilyl)acetamide (BSA)-induced tautomerization, affording trivalent phosphorus compounds, which function as the actual ligands.[8] In the course of our studies on asymmetric synthesis of all-carbon quaternary stereocenters using DIAPHOXs, γ-acetoxy-α,β-unsaturated carbonyl compounds stood out as potential substrates.[9] Asymmetric allylic alkylation of γ-acetoxy-α,β-unsaturated carbonyl compounds with β-keto esters gives characteristic reaction adducts with three different carbonyl groups. The densely functionalized structure is useful for natural product synthesis.[10] Despite the versatility, there is no direct access to this class of chiral building blocks. Herein, we report the enantioselective construction of all-carbon quaternary stereocenters using Pd-catalyzed asymmetric allylic alkylation of γ-acetoxy-α,β-unsaturated carbonyl compounds with cyclic β-keto esters as prochiral nucleophiles.



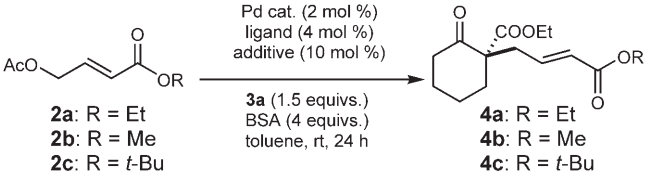
(S,R_P)-R-DIAPHOX
1a: R = Ph
1b: R = 1-Np[a]
1c: R = 2-Np[a]

[a] Np = naphthyl.

(S,R_P)-Ph-(*p*-MeO)DIAPHOX

Figure 1. Structure of P-chirogenic diaminophosphine oxides: DIAPHOXs.

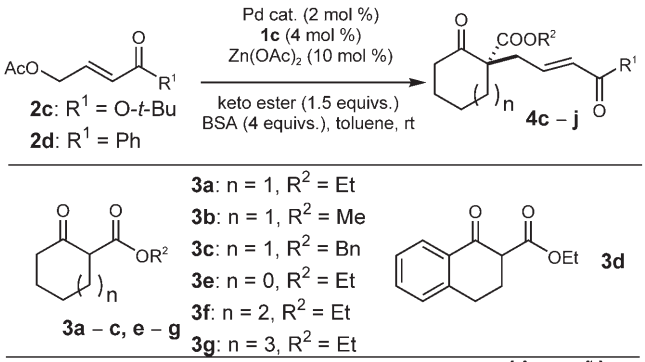
Table 1. Optimization of the reaction conditions.



Entry	Acetate	Additive	Ligand	Yield [%][a]	ee [% ee][b]
1	**2a**	———	**1a**	No Reaction	———
2	**2a**	LiOAc	**1a**	44	4
3	**2a**	$Mg(OAc)_2 \cdot 4\ H_2O$	**1a**	83	64
4	**2a**	$Zn(OAc)_2$	**1a**	89	78
5	**2b**	$Zn(OAc)_2$	**1a**	59	79
6	**2c**	$Zn(OAc)_2$	**1a**	99	91[c]
7	**2c**	$Zn(OAc)_2$	**1b**	97	95[c]
8	**2c**	$Zn(OAc)_2$	**1c**	99	95[c]
9	**2c**	$Zn(OAc)_2$	**1d**	99	92[c]

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The absolute configuration was determined to be *S*. See the supporting information for details.

Table 2. Asymmetric allylic alkylation using various substrates.



Entry	Acetate/ Keto Ester	Product	Time [h]	Yield[a] [%]	ee[b] [%]
1	**2c/3a**	**4c**	24	99	95 (*S*)
2	**2c/3b**	**4d**	48	99	91
3	**2c/3c**	**4e**	24	99	92
4[c]	**2c/3d**	**4f**	48	92	93
5	**2d/3a**	**4g**	24	97	90 (*S*)
6[d]	**2c/3e**	**4h**	48	74	90
7	**2c/3f**	**4i**	48	99	75
8	**2c/3g**	**4j**	48	98	68

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] 5 mol % of the Pd catalyst was used.
[d] **1d** was used as the ligand.

We initially examined the catalytic asymmetric allylic alkylation of γ-acetoxycrotonic acid ethyl ester (**2a**) with ethyl 2-oxocyclohexanecarboxylate (**3a**) (Table 1). First, we investigated the effect of the addition of acetate salt using 1 mol % of $(\eta^3\text{-}C_3H_5PdCl)_2$ and 4 mol % of (S,R_P)-Ph-DIAPHOX (**1a**). Similar to the previous case, $Zn(OAc)_2$ was the best additive for asymmetric induction.[7] Further optimizations for the ester substituent of γ-acetoxycrotonates were preformed in the presence of $Zn(OAc)_2$, revealing that the substrate with a *tert*-butyl ester (**2c**) gave the best selectivity. The effect of the ligand structure was also investigated using **1b**–**1d**, and the corresponding product was obtained in 99% yield with 95% ee, using (S,R_P)-2-Np-DIAPHOX (**1c**) as the ligand.

The scope and limitations of different substrates were further examined using these efficient conditions (Table 2). When 2 to 5 mol % of the catalyst was used, asymmetric allylic alkylation of **2c** using prochiral nucleophiles with a six-membered ring proceeded at room temperature to provide the corresponding products in excellent yield with high enantioselectivity (91–95% ee). The reaction system was also applicable to γ-acetoxy-α,β-unsaturated ketone **2d**, affording the corresponding products in good yield with high enantioselectivity (90% ee). In addition, nucleophiles with five-, seven-, and eight-membered rings were investigated using **2c** as the substrate. As a result, the corresponding products were obtained with modest to high enantioselectivity; 90% ee (five-membered ring), 75% ee (seven-membered ring), and 68% ee (eight-membered ring), with the use of **1d**, **1c**, and **1c** as the ligand, respectively. It is noteworthy that no conjugate addition of the nucleophile to the substrate occurred in this catalytic process. To the best of our knowledge, this is the first application of γ-acetoxy-α,β-unsaturated carbonyl compounds to Pd-catalyzed asymmetric allylic alkylation for construction of quaternary carbons.

In conclusion, we have achieved the Pd-catalyzed asymmetric allylic alkylation of γ-acetoxy-α,β-unsaturated carbonyl compounds with cyclic β-keto esters as the prochiral nucleophiles. This contribution provides a new strategy for the synthesis of functionalized chiral synthons with an all-carbon quaternary stereocenter. Further studies, including diastereoselective modification of the reaction adducts, are currently in progress.

Experimental Section

Typical Procedure for the Pd-Catalyzed Asymmetric Allylic Alkylation

To a stirred mixture of $(\eta^3\text{-}C_3H_5PdCl)_2$ (9.2 mg, 0.025 mmol, 2 mol % of Pd.), **1c** (44.1 mg, 0.1 mmol, 4 mol %), acetate **2c** (0.50 g, 2.5 mmol), keto ester **3a** (0.59 mL, 3.75 mmol), and $Zn(OAc)_2$ (45.9 mg, 0.25 mmol) in toluene (16.7 mL) was added BSA (2.47 mL, 10 mmol) at room temperature, and the reaction mixture kept stirring at the same temperature, under an

argon atmosphere. After 24 h, the mixture was concentrated under vacuum, and the obtained residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 20/1) to give **4c** as colorless oil; yield: 0.77 g (99%, 95% ee). IR (neat): $\nu = 2968, 2936, 2868, 1714, 1653, 1455, 1367, 1253, 1157\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.25$ (t, $J = 7.2$ Hz, 3H), 1.46 (s, 9H), 1.43–1.55 (m, 1H), 1.66–1.75 (m, 3H), 2.02–2.05 (m, 1H), 2.41–2.51 (m, 4H), 2.69 (ddd, $J = 1.2$ Hz, 7.6 Hz, 14.0 Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 5.74 (ddd, $J = 1.2$ Hz, 1.2 Hz, 15.2 Hz, 1H), 6.74 (ddd, $J = 7.6$ Hz, 15.2 Hz, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 14.0, 22.4, 27.3, 28.0\ (\times 3), 36.0, 37.3, 40.9, 60.5, 61.4, 80.1, 126.2, 142.1, 165.2, 171.0, 206.7$; FAB-LR-MS: $m/z = 311$ (MH^+), 255 ($MH^+ - 56$); $[\alpha]_D^{23}$: -81.7 (c 1.00, $CHCl_3$, 95% ee); FAB-HR-MS: calcd. for $C_{17}H_{27}O_5$: 311.1859; found: 311.1873.

The enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL, AD-H, 2-propanol/hexane, 5/95, flow rate 0.3 mL/min, retention time: 22.5 min [(*R*)-isomer] and 23.8 min [(*S*)-isomer], detected at 254 nm).

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