# Metallophosphites as Umpolung Catalysts: The Enantioselective Cross Silyl Benzoin Reaction

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Polarity reversal (reactivity umpolung) of functional groups is a powerful synthetic strategy that has been widely employed by organic chemists.[1] The benzoin condensation is the archetypal catalytic reaction in which carbonyl polarity is inverted via an intermediate that functions as an acyl anion equivalent. To date, this reactivity pattern has only been realized catalytically with cyanide anion or heteroazolium carbenes.[2,3] Herein, we introduce metallophosphites as a new class of catalyst capable of achieving this challenging bond construction and concurrently describe the development of chiral phosphites that facilitate nonenzymatic[4,5] asymmetric cross benzoin reactions (eq 1).

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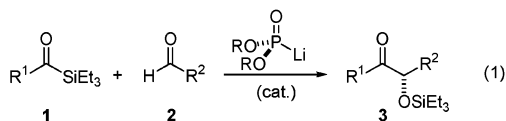
The α-hydroxy carbonyls that result from benzoin or acyloin condensations are desirable building blocks and comprise a structural motif that is common among natural products. Thermodynamic constraints have limited the development of catalyst-controlled asymmetric benzoin condensations to homocoupling, with the benchmark recently established by Enders.[6] In a recent publication, we described kinetically controlled, regiospecific cross silyl benzoin reactions between acylsilanes **1** and aldehydes **2** that are catalyzed by KCN.[7] The proposed mechanism (Scheme 1) suggests that any potential catalyst for this reaction must function at different stages in the catalytic cycle as a nucleophile (**1 → 1a**), anion stabilizing group (**1a → 1b**), and leaving group (**1d → 3**).

We speculated that metallophosphites ((RO)₂P(O)M)) might meet these requirements. Important precedent for this hypothesis was provided by Takeda, who demonstrated that lithium diethyl phosphite reacts stoichiometrically with acylsilane **1** to give carbanion **1b** after Brook rearrangement.[8–10] Further, Zimmer had shown that the addition of (silyloxy)phosphonate anion **1b** (Nu = P(O)(OEt)₂) to aldehydes can afford silyl benzoin products **3**.[11] Chiral phosphorous acid derivatives are well developed as ligands for a variety of metal-catalyzed asymmetric reactions[12] and serve as effective auxiliaries for asymmetric 1,2-additions to aldehydes and imines and 1,4-addition to Michael acceptors;[13–15] however, to the best of our knowledge, no phosphite has been employed as an enantioselective nucleophilic catalyst.

The concept of this new catalytic reaction was verified by preliminary experiments. Lithium diethyl phosphite formed in situ via the deprotonation of diethyl phosphite with *n*-BuLi catalyzes the cross silyl benzoin reaction between benzoyl triethylsilane and *p*-anisaldehyde to afford the corresponding silyloxy benzoin in 60% yield (Table 1, entry 1). Although the phosphite derived from commercially available (*R*)-BINOL showed no catalytic activity (entry 2), the possibility of chirality transfer in the process was confirmed by the same reaction with enantiopure (*R*,*R*)-TADDOL-
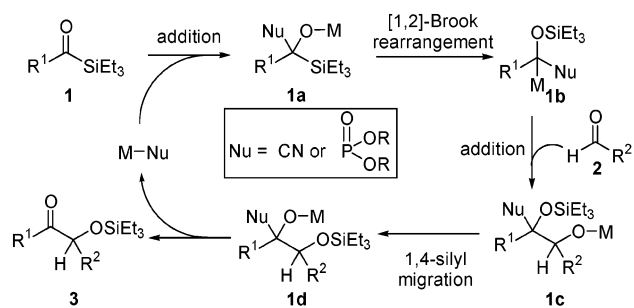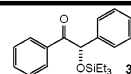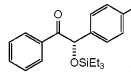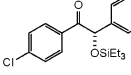
Scheme 1
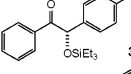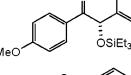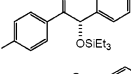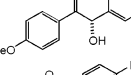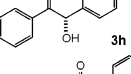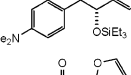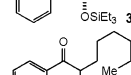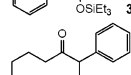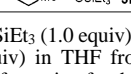
Table 1. Evaluation of Phosphite Catalysts

entry	phosphite		% ee[a]	% conv.[b]
1	(EtO)₂P(O)H	**4a**	-	100 (60)[c]
2		**4b**	-	<5
3		**4c** Ar = Ph	41	100
4		**4d** Ar = 2-MePh	77	<20
5		**4e** Ar = 2-naphthyl	58	<20
6		**4f** Ar = 2-FPh	90	100
7		**4g** Ar = 2,6-F₂Ph	74	<60
8		**4h** Ar = F₅Ph	-	<5
9		**4i** Ar = 2-CF₃Ph	-	<5
10		**4j** R¹ = Me, R² = Ph	75	<80
11		**4k** R¹,R² = (CH₂)₄	86	100
12		**4l** R¹,R² = (CH₂)₅	88	100
13		**4m** Ar = Ph[d]	76	100
14		**4n** Ar = 2-FPh	66	100

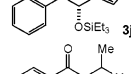[a] Determined by CSP−SFC using a (*S,S*)-Whelk-O1 column. [b] Conversion determined by ¹H NMR spectroscopy or CSP−SFC. [c] Isolated yield of analytically pure material. [d] Reaction conducted in Et₂O.

derived phosphite (entry 3).[15] TADDOL is an attractive platform for catalyst development because of the ability to easily tune the

Table 2. Scope of the Asymmetric Catalytic Cross Silyl Benzoin Reaction[a]

entry	product[b]	cat. 4f (mol %)	% ee[c]	% yield[d]
1	**3a**	7.5	82	84
2	**3b**	7.5	82	75
3	**3c**	7.5	87	82
4	**3d**	5	91	87
5	**3e**	7.5	88	83
6	**3f**	7.5	90	83
7	**3g**	10	83[e]	79
8	**3h**	5	81[e]	80
9	**3i**	12.5	86	86
10	**3j**	7.5	85[e]	65
11	**3k**	15	73	78
12	**3l**	20	41	88
13	**3m**	20	67	72

[a] $R^1C(O)SiEt_3$ (1.0 equiv), R^2CHO (1.5 equiv), phosphite **4f**, and *n*-BuLi (0.2–0.4 equiv) in THF from 0 to 25 °C. Reaction time = 0.5 h. See Supporting Information for details. [b] The (*S*)-configurations of silyl benzoins **3a**, **3c**, **3d**, **3e**, and **3k** were assigned by chemical correlation to compounds of known absolute configuration. Other aryl–aryl silyl benzoin products were assigned by analogy. [c] Product ratios determined by CSP–SFC using a (*S*,*S*)-Whelk-O1 or Chiralcel OD column unless otherwise noted. [d] Isolated yield of analytically pure silyloxy ketones or hydroxy ketones. [e] Selectivity determined by CSP–SFC using a Chiralpak AS column after hydrolysis of the product TES ether.

steric and electronic characteristics of the resultant phosphite.[16] Bulkier TADDOL phosphites improved the selectivity moderately, but exhibited somewhat limited reactivity (entries 4 and 5). The tetra(*o*-fluorophenyl)-TADDOL phosphite **4f** provided the best combination of enantiocontrol and reactivity (entry 6). More powerful electron-withdrawing groups caused a dramatic drop in reactivity (entries 7–9). All other variations on the TADDOL phosphite backbone led to a decrease in selectivity relative to **4f** (entries 10–14). THF was the best solvent among those screened

(THF, Et_2O, toluene, and dioxane) in terms of both reactivity and selectivity.

Phosphite **4f** catalyzes the asymmetric cross benzoin reaction between a number of acylsilanes and aldehydes. As summarized in Table 2, the reaction is quite general for aryl acylsilanes and aryl or heterocyclic aldehydes with good to excellent yields (65–87%) and enantioselectivities (81–91% ee) (entries 1–10). The more challenging aryl–alkyl′ and alkyl–aryl′ benzoin adducts were obtained in good yields (72–88%) and reasonable selectivities (41–73% ee) (entries 11–13). At our current level of optimization, the use of excess *n*-BuLi relative to the phosphite ensures complete conversion; this may be a reflection of the sensitivity of the reaction to moisture. All of the reactions in Table 2 were complete within 0.5 h at ambient temperature.

Chiral metallophosphites may be useful templates for other asymmetric transformations that proceed via umpoled intermediates such as **1b**. Current efforts in our laboratory are addressing this issue. Results from this research and a full account of the new enantioselective cross benzoin reaction described herein will be the topics of future publications.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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