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# Metallophosphite-Catalyzed Asymmetric Acylation of α,β - Unsaturated Amides

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## Abstract

The *l*-menthone-derived TADDOL phosphite **6b** catalyzes highly enantioselective conjugate additions of acyl silanes to α,β-unsaturated amides. *p*-Methoxybenzoyl cyclohexyldimethylsilane adds to a variety of *N*,*N*-dimethyl acrylamide derivatives in the presence of the lithium salt of **6b**. In many instances the α-silyl-γ-ketoamide product undergoes facile enantioenrichment (to 97–99% ee) upon recrystallization. Desilylation with HF·pyr affords the formal Stetter addition products. Baeyer–Villiger oxidation of the desilylated γ-ketoamides affords useful ester products. An X-ray diffraction study of **6b** reveals that the isopropyl group of the menthone ketal influences the position of the *syn*-pseudoaxial phenyl group in the TADDOL structure. Through a crossover experiment, the silicon migration step in the reaction mechanism is shown to be strictly intramolecular.

## Introduction

The conjugate addition of acyl anion equivalents to α,β-unsaturated carbonyls is a useful and direct approach to the synthesis of 1,4-dicarbonyl compounds that can simultaneously introduce two new stereocenters.[1] The prototypical catalytic reaction type involves the use of cyanide or heterazolium carbenes as umpolung catalysts.[2–4] Employing scalemic versions of the latter, the asymmetric intramolecular Stetter reaction was recently realized as a useful transformation by Enders and coworkers.[5,6] The transformation has undergone some significant improvements in enantioselectivity and scope in a body of work by Rovis and co-workers that now stands as the benchmark in this family of reactions.[7–12] Their optimized process lends itself to a number of α,β-unsaturated ester and ketone acceptors delivering the annulated products in high yield and enantioselectivity; however, extension to asymmetric intermolecular alkene acylation has generally proven challenging. Enders was the first, to our knowledge, to successfully investigate this variant, achieving the addition of butanal to chalcone in 4–29% yield and 30–39% enantiomeric excess;[13] these results represent the current state-of-the-art.

In parallel with the development of aldehydes as acyl donors for conjugate additions, acyl silanes have shown promise as suitable pronucleophiles in conjugate addition reactions. As in the classic Stetter reaction, cyanide and heterazolium carbenes can trigger the needed umpolung reactivity: $^{-}$CN-catalyzed addition of acyl silanes to cyclic enones and acyclic acrylates was demonstrated by Degl'Innocenti,[14] while carbene catalysis was shown by Scheidt to be effective for the acylation of α,β-unsaturated esters and ketones.[15,16] Since the initiating steps in these catalytic processes involving acyl silanes are presumed to be carbonyl addition and [1,2]-Brook rearrangement,[17,18] a pressing question related to catalysis was

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**Supporting Information Available:** Experimental procedures, compound characterization data, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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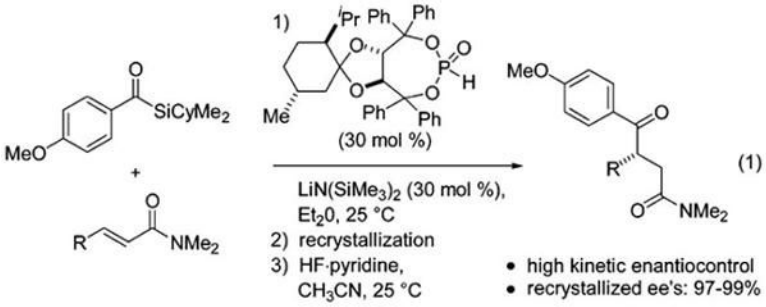
whether other entities might trigger these events. Indeed, Reich and Takeda had already shown that lithium phosphites add to acyl silanes and cause silicon migration.[19,20] The latter study was particularly relevant since a pendant α,β-unsaturated ester was employed to trap the nascent (siloxy)phosphonate anion.[21] The work of Reich and Takeda was instrumental to our development of chiral metallophosphites as nucleophilic catalysts for aldehyde and alkene acylation.[22,23] We recently demonstrated a preliminary asymmetric variant of the alkene acylation reaction that proceeded in 67% yield and 50% enantiomeric excess using the Enders (*R*,*R*)-TADDOL-phosphite **1-Ph**.[24,25] From that platform we hypothesized that more highly enantioenriched 1,4-dicarbonyl products could be obtained through tuning of the phosphite catalyst and reagent functional groups. This article details the development of an effective asymmetric metallo-phosphite-catalyzed intermolecular addition of acyl silanes to α,β-unsaturated amides that can be achieved under mild reaction conditions in good yield and high enantioselectivity (eq 1).




## Results and Discussion

### I. Optimization Studies

**Phosphite Structure—**The asymmetric cross silyl benzoin reaction developed in our laboratory[22] exhibited significant enantioselectivity enhancement through varying the aromatic groups on the (*R*,*R*)-TADDOL-phosphite (**1-Ar**). Due to this positive effect, our first instinct was to examine those electronic modifications on the phosphite in the 1,4-addition of benzoyl dimethylphenylsilane **2** to morpholinocinnamide **3** (Scheme 1). Electron-withdrawing substituents on **1** gave very low conversion, but in all reactions, neither electron-withdrawing nor electron-donating aromatic groups gave a significant boost in enantioselectivity.

Another candidate for site modification in the catalyst architecture was the ketal backbone. In previous studies, we had observed minimal effect in changes at this site;[22] however, we were pleased to find that replacement of acetone with *l*-menthone in the initial ketalization using either L- or D-diethyl tartrate afforded, after Grignard addition and phosphinylation, diastereomeric phosphite catalysts **6a** and **6b** (Figure 1) that exhibited notably higher levels of enantiocontrol in the addition of **2** to **3**. Although the menthone tartrate has been reported by Seebach,[26] to the best of our knowledge, our preparation of **6a** and **6b** constitutes the first synthesis of a menthone-based TADDOL.[25] The therapeutic effects of this modification were noted in not only the enantiomeric excess of **5** (−60% ee using **6b**, Table 1, entry 2) but also the improved *anti*/*syn* selectivity for the intermediate α-silyl-γ-ketoamide **4** (**6b**: *anti*/*syn* = 20:1; **1-Ph**: *anti*/*syn* = 10:1). The latter point impacts the former since we had previously demonstrated that *anti* and *syn* diastereomers possess the *opposite* absolute configuration at the phenyl-bearing stereocenter and that desilylation of the mixture results in erosion in the enantiomeric excess of **5**.[23]

**Amide—**The impact of the amide structure on enantioselec-tivity and reactivity was probed through an examination of eleven cinnamides; a complete summary of this study may be found

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in the Supporting Information. Pyrrole, pyrazole, and Weinreb cinnamides failed to provide any acylation product. In fact, of the amides surveyed, only *N*,*N*-dimethylcinnamide (**7**) exhibited significant improvement relative to the morpholinocinnamide **3** in both conferred enantiocontrol (71% ee using phosphite **6b**) and diastereoselectivity for the derived α-silyl-γ-ketoamide **9** (Scheme 2). The reaction proceeded at a somewhat slower rate and product yield was lower (40%, Table 1, entry 3), but only a single diastereomer of the α-silyl-γ-ketoamide **9** could be distinguished by $^1$H NMR spectroscopy (*anti*/*syn* > 30:1).

**Acyl Silane—**Attention was then directed at improving the enantiomeric excess and yield for the alkene acylation through modification of the acyl donor. Our experiments in this vein revealed that the identity of the silyl moiety was crucial for maximizing enantiocontrol and that the aryl group of the acyl silane was the key in modulating reactivity. The addition of benzoyl triethylsilane to *N*,*N*-dimethylcinnamide (**7**) catalyzed by **6b** gave the product α-silyl-γ-ketoamide as one distinguishable diastereomer by $^1$H NMR spectroscopy and the desilylated γ-ketoamide product **8** in 88% enantiomeric excess (Table 1, entry 4). Further increases in the steric demand of the silyl group (benzoyl triisopropylsilane, benzoyl trihexylsilane, benzoyl *tert*-butyldimethylsilane) resulted in dramatic decreases in reactivity. The use of benzoyl cyclohexyldimethylsilane[27] furnished **8** in comparable enantioselectivity to PhC(O)SiEt$_3$ but conferred the added bonus of crystallinity to the intermediate α-silyl-γ-ketoamide. This characteristic was found to be relatively common (vide infra) and was used advantageously in purification and upgrades in product enantiomeric excess. Although the boost in enantioselectivity using PhC(O)SiEt$_3$ and PhC(O)-SiCyMe$_2$ was encouraging, product yields were still unacceptably low. In probing this issue, we were fortunate to discover that substitution of the phenyl group of the acyl silane with a *para*-anisyl group reduced reaction times, provided the needed increase in yield, and had little effect on the enantioselectivity. Specifically, phosphite **6b** catalyzed the efficient conjugate addition of *para*-methoxybenzoyl cyclohexyldimethylsilane **10** to cinnamide **7**; desilylation of an aliquot of α-silyl-γ-ketoamide **11** indicated that the kinetic enantioselectivity for the initial addition was 95:5 (Scheme 3). The remainder of amide **11** was recrystallized from hot hexanes and upon desilylation afforded **12a** in 99% ee and 68% yield.

The key experiments in the reaction evolution are summarized in Table 1, and a more extensive tabulation can be found in the Supporting Information. All reactions were run on a 100 mg scale in a glovebox using 20 mol % of the phosphite catalyst and base, lithium hexamethyldisilazide. The optimized reagents were also tested using catalyst **1-Ph** (entry 7) for a direct comparison to the menthone phosphite **6b**, and phosphite **6a** (entry 9) was employed to demonstrate that both product enantiomers can be obtained. A final operational modification was made involving the deprotection step: the use of tetra-*N*-butylammonium fluoride (TBAF) was occasionally found to cause erosion in product enantioselectivity depending on contact time with the substrate. Desilylation using HF·pyridine in acetonitrile gave comparable yields and consistent enantiose-lectivities (entries 8,9).

After an optimized reaction protocol had been established for the asymmetric conjugate addition of acylsilanes to α,β-unsaturated amides in the glovebox, it was necessary from a practicality standpoint to achieve those yields and enantioselectivities outside of the glovebox. Our initial efforts resulted in inconsistent results with incomplete conversion arising as a common problem even under nominally anhydrous and anerobic conditions. Separation and isolation of materials from these reactions and identification of them by $^{31}$P spectroscopy and mass spectrometry revealed the presence of (1) the conjugate addition product between the phosphite and unsaturated amide[24] and (2) the (siloxy)phosphonate resulting from quenching of the Brook rearrangement product. The precursors to these byproducts are understandably sensitive to traces of proton sources. The use of excess base was sufficient in our cross benzoin studies to achieve a simple reaction protocol and avoid this problem, but conditions employing

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excess base gave nearly racemic product in the current study. To achieve full conversion outside of the glovebox, we found it optimal to conduct reactions on at least a 200 mg scale using 30 mol % of phosphite and 30mol % of $LiN(SiMe_3)_2$ at room temperature. This gave a simple and reproducible protocol and also simplified recrystallization of the silylated product.

## II. Substrate Scope and Limitations

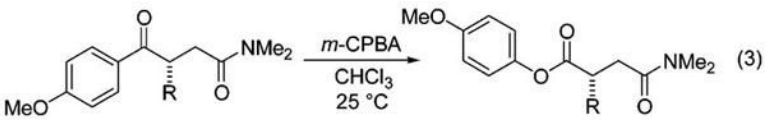
The reaction scope with respect to the Michael acceptor was then analyzed employing the aforementioned reaction conditions. An aliquot from each reaction was removed and desilylated to determine the kinetic enantioselectivity for the addition. When possible, the remaining α-silyl-γ-ketoamide was recrystallized. Deprotection with HF·pyridine in acetonitrile afforded γ-ketoamides **12a**–**k**. Yields and enantioselectivities of the final products are listed in Table 2.

The alkene acylation is applicable to α,β-unsaturated amides containing both electron-donating (entries 2–4) groups and electron-withdrawing groups (entries 6–8) in the β-position of the Michael acceptor affording the product in reasonable yields and high enantioselectivities except for the strongly electron-donating furyl substituent (entry 5). β-Alkyl amides also undergo productive coupling with somewhat lower product enantioselectivities (entries 10–11). While the scope is good for the Michael acceptor, a notable limitation of this acylation protocol in its current form is its inability to successfully couple alkyl acyl silanes (RC(O)SiR′$_3$, R = alkyl) with unsaturated amides in yields > 10%. Since the metallophosphite addition and Brook rearrangement steps have been demonstrated for alkyl acyl silanes,[22] this lack of reactivity is apparently due to the inability of the (silyloxy)phosphonate anion to participate in conjugate addition.

The optimized reaction conditions described above work well on a reasonable laboratory scale. On a 5-g scale, the addition of **10** to *N*,*N*-dimethylcinnamide catalyzed by **6b** gives the α-silyl-γ-ketoamide **11** in >99% enantiomeric excess after crystallization. Deprotection with HF·pyridine and recrystallization give the enantiopure γ-ketoamide **12a** in 61% yield for the two steps.

## III. Product Manipulation and Stereochemistry

Table 1 suggests, and experiments with other acyl silanes confirm, that the *p*-anisyl substitutent in **10** is needed for high yield and enantioselectivity. We viewed this apparent limitation as an opportunity to develop useful second-stage reactions involving the acylation products. In particular, we considered that oxidation of the $C_{aryl}$–$C_{carbonyl}$ bond would provide a broader selection of 1,4-dicarbonyl compounds with more flexibility for subsequent manipulation. Such Baeyer–Villiger reactions of (methoxyphenyl)ketones in conjunction with asymmetric synthesis are well-documented.[28–32] Indeed, exposure of **12a** and **12j** to *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform resulted in oxidation of the ketones to the derived *p*-methoxyphenyl (PMP) esters **13a** and **13j**, respectively (eq 3). As expected, no loss in optical purity was observed for the ester products. The difference in the yield for **13a** relative to **13j** arises from a regioisomeric Baeyer–Villiger product in the former case.




**12a** R = Ph, 99% ee
**12j** R = Me, 89% ee

**13a** R = Ph, 82% yield, 99% ee
**13j** R = Me, 95% yield, 89% ee

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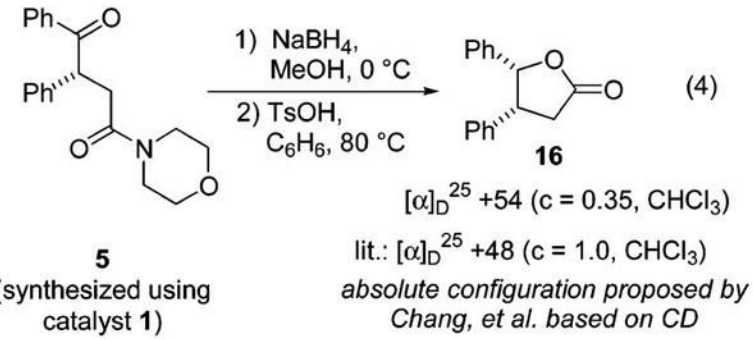
The PMP esters are useful compounds that permit differentiation of the two carbonyl groups and provide access to other useful building blocks (Scheme 4). Transesterification of **13a** with methanol occurs to afford the corresponding methyl ester **14** with little racemization. Ester **13a** undergoes chemoselective reduction with $NaBH_4$ to give γ-hydroxyamide **15** in >95% yield with negligible loss in enantiopurity.

The absolute configuration of **15** (and thence **13a** and **12a**) was established through comparison of its optical rotation to that reported in the literature for the 3(*R*) isomer.[33] This assignment was cross-verified through an X-ray diffraction study of enantiomerically pure **12f**; this amide also possessed the (*R*) configuration.[34] These stereochemical proofs are at odds with the one provided in our original communication for compound **5**. That analysis involved the conversion of γ-ketoamide **5** to the γ-lactone **16**, whose absolute stereostructure had been previously proposed on the basis of CD studies on related compounds (eq 4).[35] The discrepancy between that assignment and the stereochemical assignments established in this article through both chemical correlation and X-ray crystallography suggests either (1) the stereochemical assignment made by Chang et al. (and by corollary our assignment of **5**) is incorrect or (2) there is a turnover in absolute stereochemical preference for acyl silane/amide combination **2**/**3** versus **7**/**10**. Difficulty in obtaining **5** in high enantiomeric excess has so far precluded the use of derivatization and X-ray crystallography to resolve this issue. The absolute configuration of **5** must therefore be considered tentative. In practice, however, the most synthetically useful and highly enantioenriched adducts described in this article (i.e., **12**) are those whose absolute stereostructures have been unambiguously determined. It is noteworthy that the topicity preference for the tartrate-based (silyloxy)phosphonate anion intermediate is the same for both aldehyde and alkene electrophiles, a fact that would seem to augur well for extension to other electrophiles.




## IV. Reaction Characteristics. Catalyst Structure

To better understand the structural features of the *l*-menthone-modified catalyst that result in enhanced enantiocontrol, we undertook X-ray diffraction studies of phosphites **1-Ph** and **6b** (Figure 2).[34] The structure of **6b** reveals that the isopropyl group of the menthone moiety is disposed approximately on the pseudo-$C_2$ axis of the catalyst tartrate framework. Further inspection indicates that the presence of the isopropyl group results in nonbonded compression of the nearby pseudoaxial phenyl group into the reaction site (i.e., toward the phosphorus atom). This is most clearly manifested in the distance between the ketal carbon and the *para* carbon of the pseudoaxial phenyl group *syn* to the isopropyl group. For **6b** this distance is 5.482 Å, while the analogous measurement for **1-Ph** gives a distance of 5.192 Å. For comparison, the distance from the ketal carbon to the *para* carbon of the pseudoaxial phenyl group *anti* to the isopropyl group in **6b** is 5.110 Å. These observations may reveal a structural basis for the enhanced enantioselectivity, since the isopropyl group appears to force one of the phenyl groups in closer proximity to the obligatory transition structure. Such transmission effects have

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been observed crystallographically in other nonacetonide TADDOL derivatives.[25] The fact that **6a** and **6b** provide opposite but equal enantioselectivity suggests that the absolute configuration of the menthone is not important, a supposition that is congruent with the position of the *iso*-propyl group on the pseudo-$C_2$ axis.

### Test for Silyl Group Transfer Pathway

A crossover experiment was designed (Scheme 5) to distinguish whether the silyl transfer in the title reaction was occurring via an intramolecular or intermolecular pathway. Phosphite **6b** was used to catalyze the reaction of *para*-methoxybenzoyl cyclohexyldim-ethylsilane (**10**) and benzoyl triethylsilane (**17**) with a single α,β-unsaturated amide, *N*,*N*-dimethylcinnamide (**7**), under conditions stated in the Supporting Information. By $^1$H NMR spectroscopy, the α-silyl-γ-ketoamides **11** and **18** were each obtained in >80% yield (versus internal standard) and to the exclusion of any intermolecular Si-transfer products.

With the confirmation that the silicon migration is intramolecular, we propose that the high *anti* diastereoselectivity[10] can be explained through consideration of some simple conformational issues. In the catalyzed alkene acylation, the reactive conformer of the acceptor is presumed to be *s-cis*.[36] Conjugate addition of the (siloxy)phosphonate anion[21] should provide the nascent lithium enolate in the favored (*Z*)-geometry. In this conformation, intramolecular retro-[1,4] Brook rearrangement[37] is expected to be strongly favored from the rear face of the enolate due to associated $A^{1,3}$ constraints (as depicted in Figure 3).

## Conclusion

High enantioselectivities can now be achieved in the catalytic intermolecular conjugate addition of acyl silanes to α,β-unsaturated amides. The reactions take place at room temperature in less than 2 h for a variety of aryl and alkyl substrates. In many cases the α-silyl-γ-ketoamides formed after the nucleophilic addition are stable, white solids that may be purified by recrystallization. This simple purification leads to useful enantioselectivity upgrades in several cases. While the catalyst loading is not optimal in the current iteration, the phosphites are trivial to prepare from cheap starting materials that are available in either antipode. The levels of enantiocontrol realized for the title reaction are the highest for any intermolecular Stetter-type reaction to date, and the products may be transformed to terminally differentiated chiral succinates.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

#### Acknowledgements

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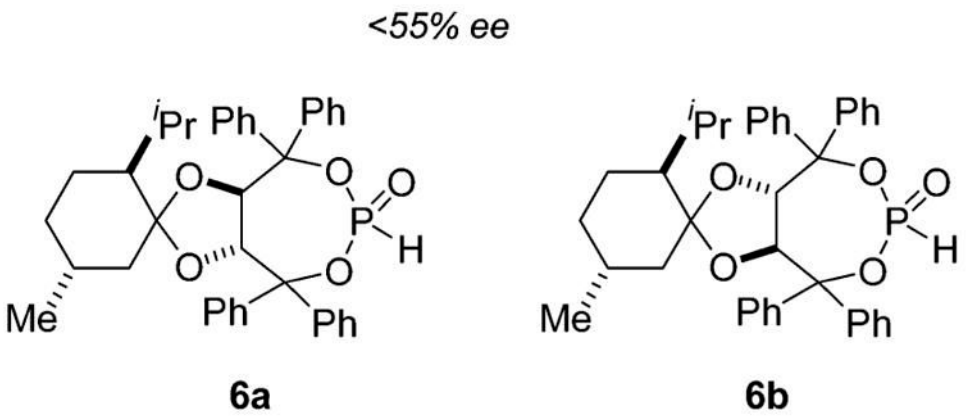


**Figure 1.**
TADDOL-phosphites containing the *l*-menthone ketal.

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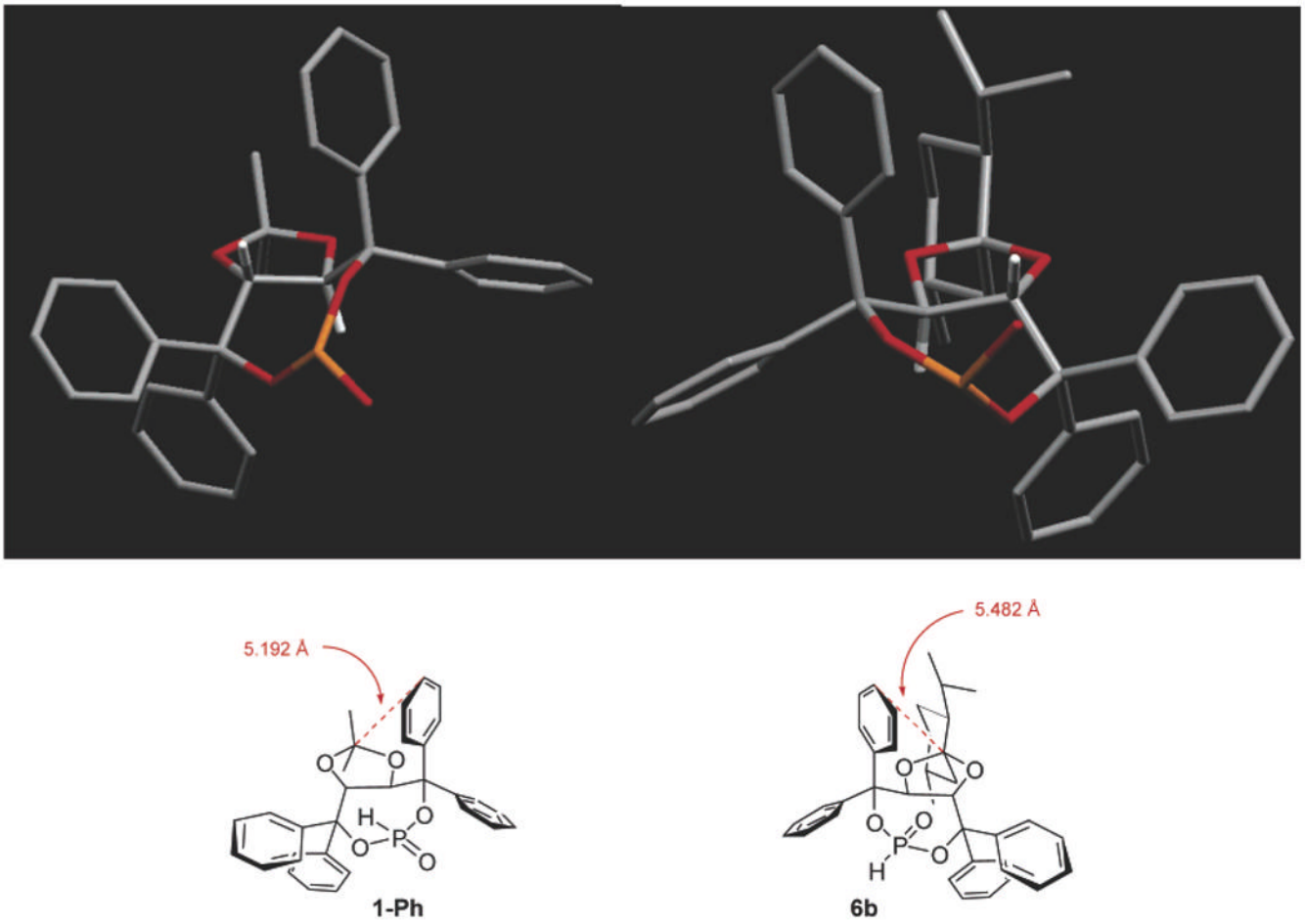


**Figure 2.**
X-ray structures of phosphites **1-Ph** and **6b**.

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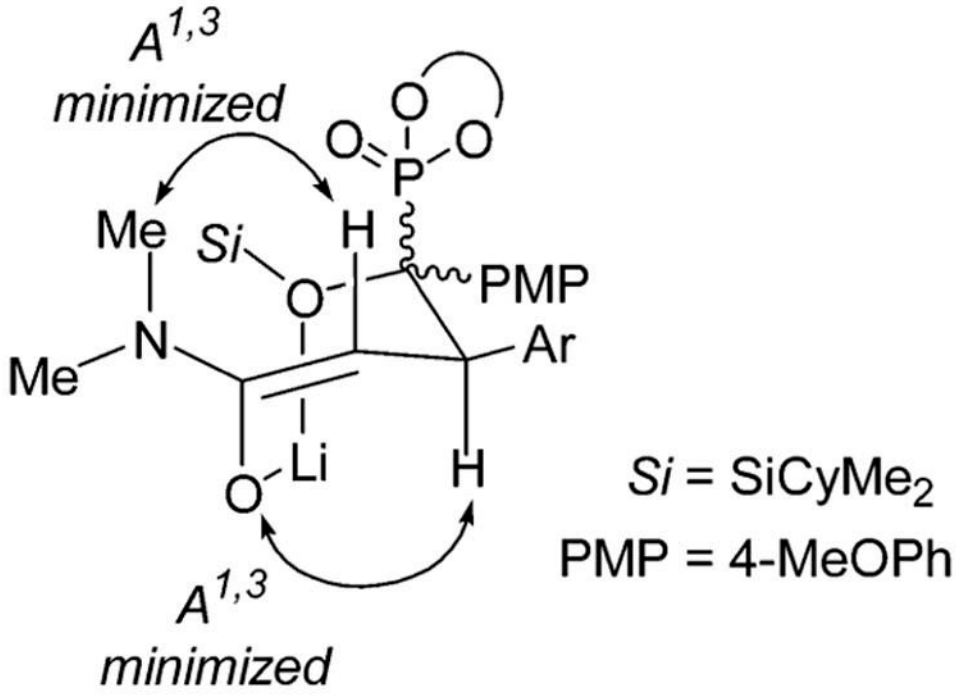
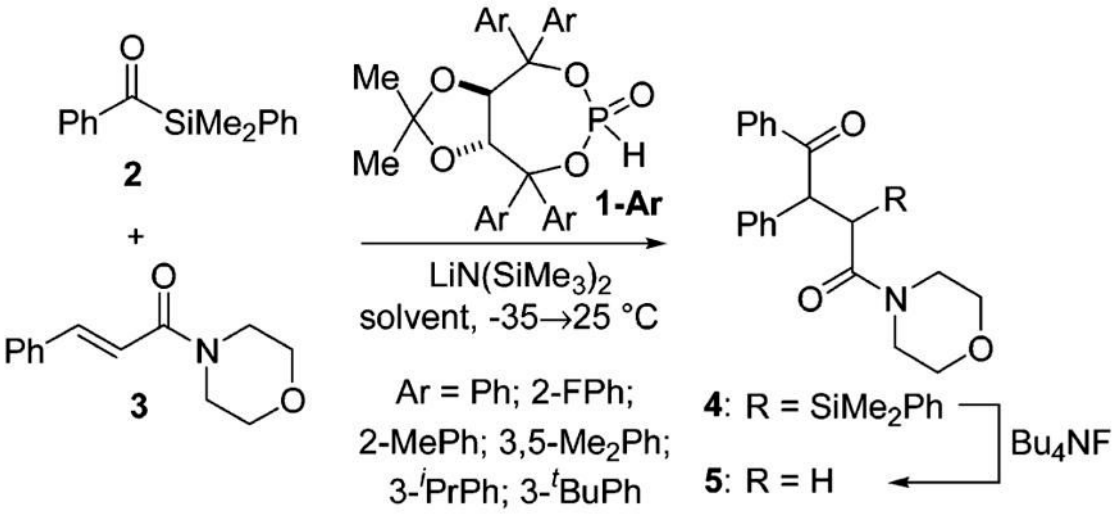



**Figure 3.**
Proposed model for *anti* diastereoselectivity.




**Scheme 1.**
Alkene Acylation Catalyzed by Phosphites **1-Ar**



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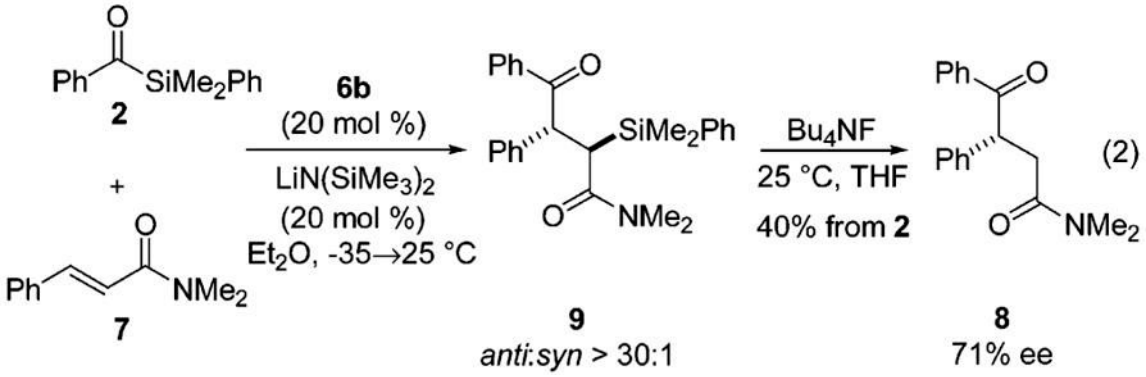


**Scheme 2.**
Enantioselective Acylation of *N*,*N*-Dimethylcinnamide



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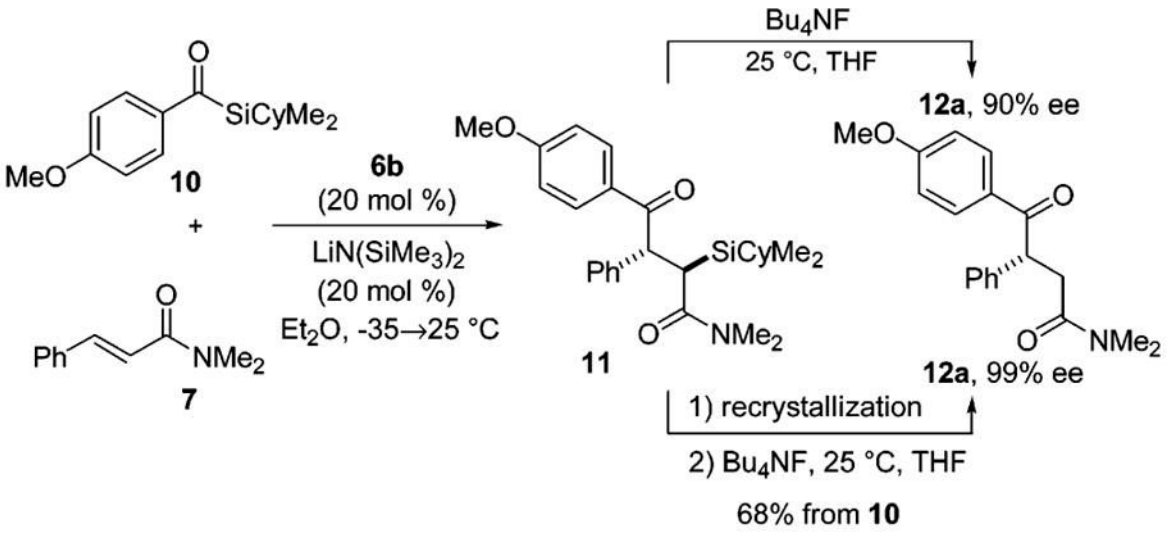


**Scheme 3.**
Recrystallization and Enantiomeric Excess Upgrade of α-Silyl-γ-ketoamide **11**



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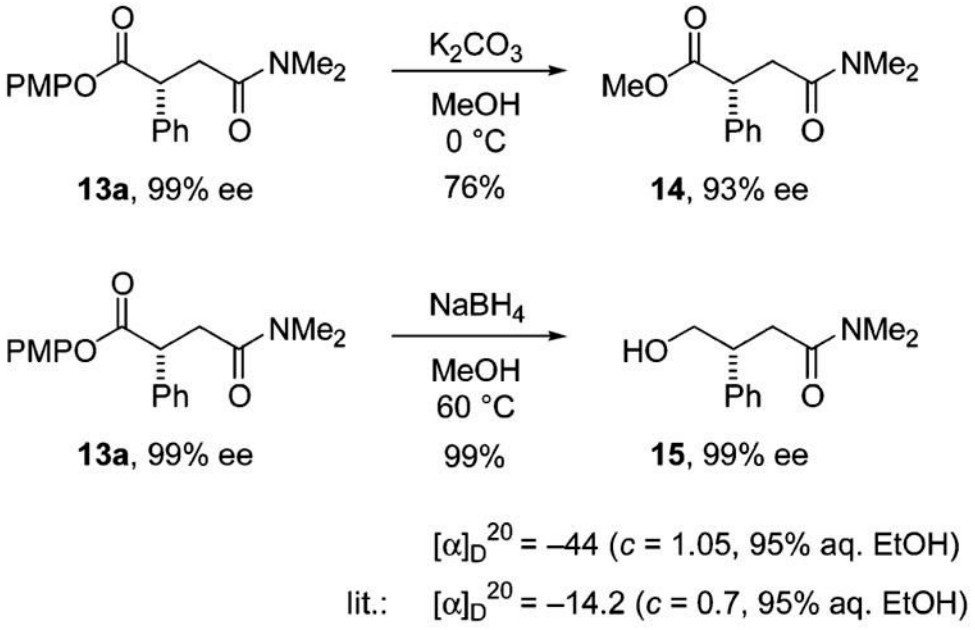


**Scheme 4.**
Synthetic Operations Involving **13a**



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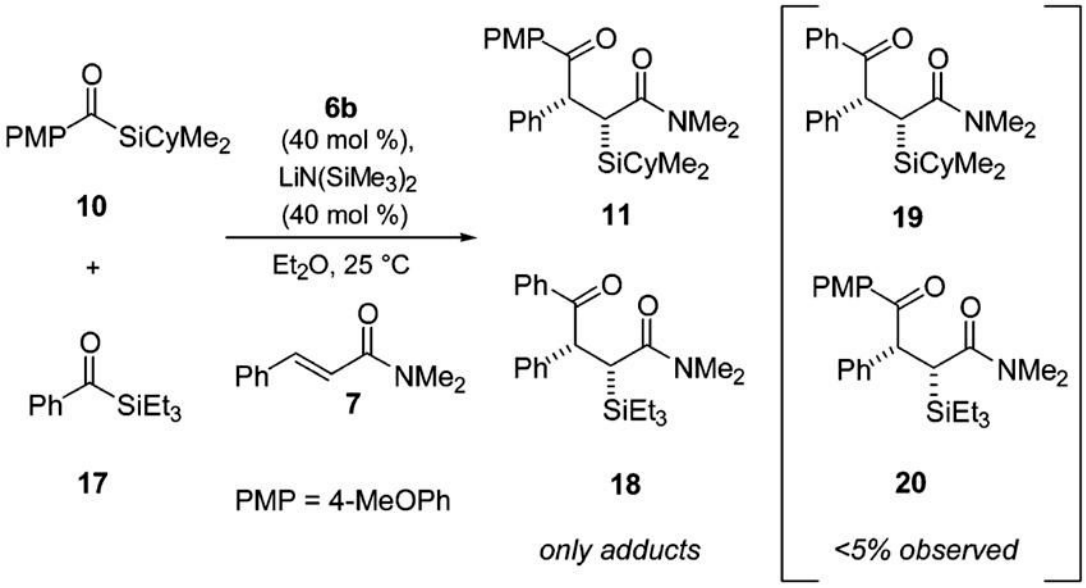


**Scheme 5.**
Crossover Experiment to Determine Silyl Group Transfer Pathway



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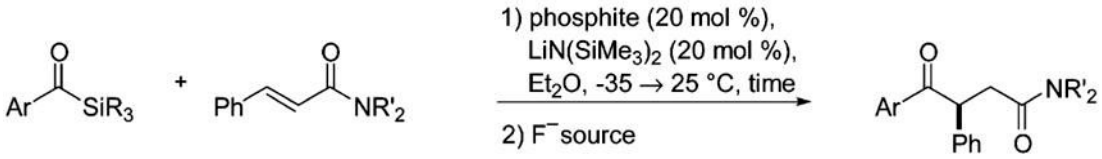
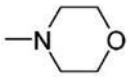
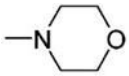
**Table 1**

Optimization Summary for Asymmetric Alkene Acylation[a]




| entry | Ar | $SiR_3$ | $NR'_2$ | phosphite | time (h) | $F^-$ source | yield (%) | %ee |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | $SiMe_2Ph$ |  | **1-Ph** | 1.0 | TBAF | 67 | 50 |
| 2 | Ph | $SiMe_2Ph$ |  | **6b** | 1.0 | TBAF | 57 | −60 |
| 3 | Ph | $SiMe_2Ph$ | $NMe_2$ | **6b** | 2.5 | TBAF | 40 | −71 |
| 4 | Ph | $SiEt_3$ | $NMe_2$ | **6b** | 2.0 | TBAF | 44 | −88 |
| 5 | *p*-MeOPh | $SiEt_3$ | $NMe_2$ | **6b** | 0.75 | TBAF | 85 | −90 |
| 6 | *p*-MeOPh | $SiCyMe_2$ | $NMe_2$ | **6b** | 0.25 | TBAF | 78 | −87 |
| 7 | *p*-MeOPh | $SiCyMe_2$ | $NMe_2$ | **1-Ph** | 1.0 | TBAF | 54 | 81 |
| 8 | *p*-MeOPh | $SiCyMe_2$ | $NMe_2$ | **6b** | 0.25 | HF·pyr | 73 | −89 |
| 9 | *p*-MeOPh | $SiCyMe_2$ | $NMe_2$ | **6a** | 1.0 | HF·pyr | 82 | 88 |

[a] $ArC(O)SiR_3$ (1.0 equiv), $PhCH{=}CHC(O)NR'_2$ (1.5 equiv), phosphite (0.2 equiv.), and $LiN(SiMe_3)_2$ (0.2 equiv) in $Et_2O$ from −35 → 25 °C for 0.25–2.0 h after slow addition of alkene and acyl silane.

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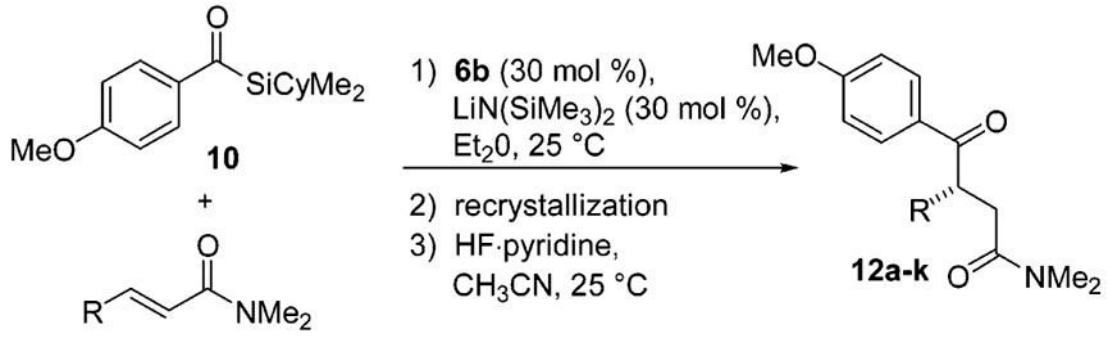
**Table 2**

Substrate Scope of Asymmetric Metallophosphite-Catalyzed Alkene Acylation[a]




| entry | R | % yield | % ee (aliquot) | % ee (12) |
|---|---|---|---|---|
| 1 | Ph (**a**) | 68 | 90 | 99 |
| 2 | *p*-MeOPh (**b**) | 63 | 92 | *b* |
| 3 | *p*-MePh (**c**) | 78 | 90 | *b* |
| 4 | *m*-MePh (**d**) | 67 | 93 | 99 |
| 5 | 2-furyl (**e**) | 15 | 24 | *c* |
| 6 | *p*-ClPh (**f**) | 66 | 95 | 98 |
| 7 | *N*-tosylindol-3-yl (**g**) | 60 | 97 | 97 |
| 8 | *p*-$CF_3$Ph (**h**)[d] | 80 | 90 | *b* |
| 9 | 2-naphthyl (**i**) | 66 | 89 | 97[e] |
| 10 | Me (**j**)[d] | 56[f] | 86[f] | *g* |
| 11 | Et (**k**)[d] | 82 | 71 | *b* |

[a] Slow addition of *p*-MeOPhC(O)SiCyMe$_2$ (1.0 equiv) and RCH=CHC(O)NMe$_2$ (1.5 equiv) to the phosphite (0.3 equiv) and LiN-(SiMe$_3$)$_2$ (0.3 equiv) in Et$_2$O at 25 °C; reaction times = 0.25–3.0 h.

[b] Attempts at recrystallization of the α-silyl-γ-ketoamide or final product (**12**) were unsuccessful.

[c] Yield was too low to attempt recrystallization.

[d] 1.1 equiv of RCH=CHC(O)NMe$_2$ was employed and was added with the acyl silane to the metallophosphite mixture.

[e] The major enantiomer was found in the mother liquor after recrystallization of the final product.

[f] Yield and % ee after separation of the major diastereomer.

[g] Recrystallization yielded little improvement in enantioselectivity.