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Pentanidium- and Bisguanidinium-Catalyzed Enantioselective Alkylations Using Silylamide as Brønsted Probase

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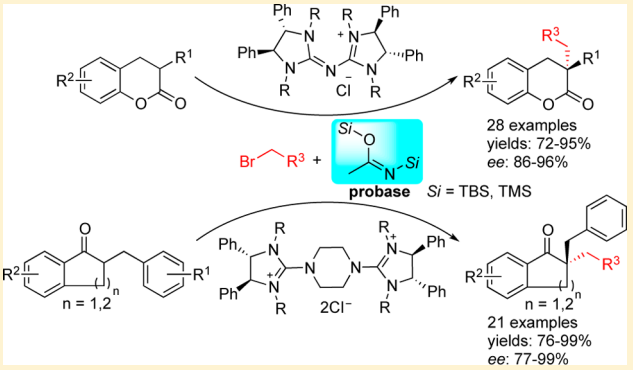
Supporting Information

ABSTRACT: Most asymmetric phase transfer reactions are Brønsted base reactions, and the inorganic bases used greatly influenced the profile of the reaction. Alkoxide salts are able to activate substrates with high p*K*a values, but background reactions are often unavoidable. On the other hand, carbonate and phosphate salts are milder, but their low basicity limits the scope of their reactions. This presents a difficult situation whereby fragile substrates such as lactone will be hydrolyzed by a stronger base but will not be activated with a weaker one. Thus, a Brønsted probase strategy is devised, in which a strong base can be generated in situ from silylamide (probase) through the use of fluoride. In this approach, the strong base produced will be transient and not be in excess, thus reducing background and side reactions. We demonstrate this strategy using pentanidinium and bisguanidinium as catalysts; highly enantioselective phase transfer alkylation of several types of substrates including dihydrocoumarin (lactone) can be achieved. We found that the probase also acts as a silylation reagent, generating silyl enol ether or silyl ketene acetal, which are key intermediates in the reaction. We further propose that hypervalent silicates form ion-pairs with pentanidinium and bisguanidinium as intermediates in the reaction, and it is through these ion-pairs that the selective enantiofacial approach of the electrophile is determined.



INTRODUCTION

Phase transfer catalysis (PTC) is an attractive approach for the preparation of enantiopure compounds on a large scale, due to its simple reaction conditions and low catalyst loading.[1,2] Many successful PTC reactions are Brønsted base reactions, and the inorganic bases used greatly influence the profile of the reaction. Alkoxide salts are able to activate substrates with high p*K*a; however, it is difficult to avoid background reactions due to the high solubility of alkoxide salts in most organic solvents as well as their nucleophilicity (Figure 1).[3] Hydroxide salts are most commonly used as they have good basicity and are less soluble in organic solvents. Esters and amides, however, are still susceptible to the nucleophilicity of hydroxide.[4] On the other hand, carbonate and phosphate salts are milder, but their low basicity limits the scope of their reactions. Hence, the challenge in many asymmetric phase transfer catalyses is to find the most appropriate base.

Many of the alkali metal amides, such as LiHMDS, LDA, and LiTMP, are commonly used in organic chemistry as strong non-nucleophilic Brønsted bases.[5] As they are soluble in organic solvents, these alkali metal amides are generally not suitable for phase transfer catalysis.[6] Kondo et al. have reported an in situ method to produce an onium amide base through fluoride anion activation of aminosilanes.[7] Encouraged by this work, we envision a Brønsted probase strategy, which a strong base can be generated in situ from silylamide through the use of fluoride (Figure 1). In this manner, the strong base will be transient and not be in excess, thus reducing background and side reactions. This approach will be particularly useful for substrates and reagents sensitive to the usual strongly basic conditions in asymmetric PTC.

Inorganic bases in PTC reaction:

base used in PTC reaction	*advantage*	*limitation*
alkoxide salts	strong basicity	good solubility strong nucleophilicity
hydroxide salts	strong basicity less solubility	strong nucleophilicity
carbonate salts phosphate salts	less nucleophilicity	weak basicity

Probase strategy (this work):

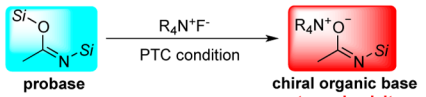


Figure 1. Silylamide as probase for phase transfer catalysis.

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RESULTS AND DISCUSSION

Enantioselective Alkylation of Dihydrocoumarins. Dihydrocoumarins have attracted much attention due to their desirable biological activities.[8] Generation of an α-quaternary carbon of hydrocoumarins is nontrivial, and there is only one known example of catalytic enantioselective synthesis.[9,10] Direct alkylation is an attractive strategy but the difficulty lies in overcoming the labile lactone, which does not survive most basic conditions.[10d] Thus, we decided to use dihydrocoumarin as the model compound to investigate our approach.

In our preliminary studies, we found that dihydrocoumarin **1a** was hydrolyzed under typical phase transfer conditions using alkoxide or hydroxides as base (Scheme 1), while no reactions were observed when carbonate or phosphate salts were used (see Supporting Information for details, Table S1). Various silylamides were evaluated as probases (Table 1), and we found that most silylamides tested did not promote the reaction (Table 1, entries 1−5). Only *bis*(trimethylsilyl)acetamide **pb4** (BSA) and trimethylsilylamine **pb1** (TMS_3N) show promising results (entries 6 and 9).

Scheme 1. PTC Alkylation of Dihydrocoumarin 1a Using Inorganic Bases

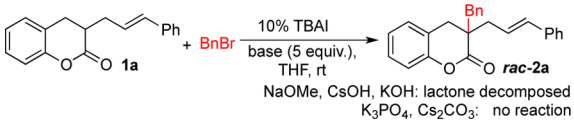
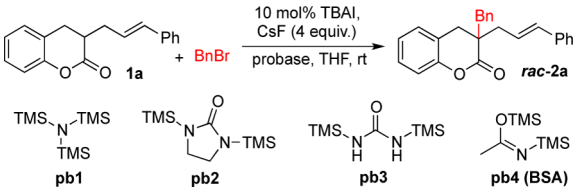


Table 1. PTC Alkylation of Dihydrocoumarin 1a Using Probases

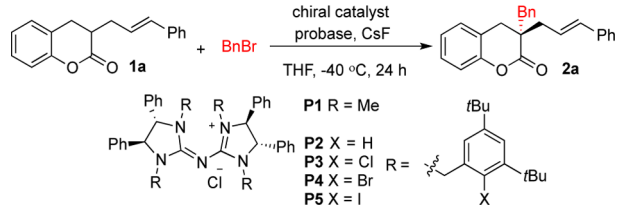


entry	probase (equiv)	yield%[a]
1	TMS_2NH (2)	NR
2	$TMSNMe_2$ (2)	NR
3	$TMSNEt_2$ (2)	NR
4	$TMSN(iPr)_2$ (2)	NR
5	*t*BuOTMS (2)	NR
6	**pb1** (2)	85
7[b]	**pb2** (5)	35
8[b]	**pb3** (5)	24
9[b]	**pb4** (5)	87

[a]Isolated yields. [b]Reaction was conducted with **1a** (0.1 mmol, 1.0 equiv), BnBr (0.2 mmol, 2.0 equiv), CsF (0.4 mmol, 4.0 equiv), and probase (0.5 mmol, 5.0 equiv) in 0.4 mL of THF and 10 mol % TBAI at room temperature for 24 h.

We have recently designed a new class of phase transfer catalyst, the pentanidium, with a conjugated guanidinium as the core structure. We have demonstrated that pentanidiums can accomplish with high enantioselectivities several reactions including conjugated addition, α-hydroxylation, and sulfenate alkylation.[11] Pentanidiums **P1** and **P2** catalyzed the enantioselective alkylation of dihydrocoumarin **1a** in the presence of **pb4** (BSA) as probase with good yields but moderate enantioselectivities (Table 2, entries 1−2). We found that when halogenated pentanidiums **P3**−**P5** were used as catalysts, high enantioselectivities were observed (entries 3−5). Halogen bonding interactions in the transition state are suspected as previously described in the sulfenate alkylation reaction.[11c] When the amounts of pentanidium **P4**, **pb4**, and CsF used were reduced, the most efficient reaction condition was found (entry 6). Probase **pb1** did not promote the reaction at −40 °C (entry 7), but when reaction temperature was raised to −20 °C, moderate enantioselectivity was observed (entry 8).

Table 2. Pentanidium-Catalyzed Enantioselective Alkylation of Dihydrocoumarin 1a



entry	catalyst (mol %)	probase (equiv)	CsF (equiv)	yield %[a]	ee[b]
1	**P1** (10)	**pb4** (5)	4	85	55
2	**P2** (10)	**pb4** (5)	4	83	40
3	**P3** (10)	**pb4** (5)	4	85	91
4	**P4** (10)	**pb4** (5)	4	88	97
5	**P5** (10)	**pb4** (5)	4	84	93
6[c]	**P4** (5)	**pb4** (3)	2	83	95
7	**P4** (10)	**pb1** (1.5)	6	trace	–
8[d]	**P4** (10)	**pb1** (1.5)	6	82	80

[a]Isolated yield. [b]Determined by chiral HPLC. [c]Reaction was carried out with **1a** (0.10 mmol), BnBr (0.20 mmol), CsF (0.2 mmol, 2.0 equiv), probase (0.3 mmol, 3.0 equiv) in 0.4 mL of THF at −40 °C for 24 h; gram-scale experiment **1a** (1.2 g, 4.5 mmol), see Supporting Information S7. [d]Reaction temperature is −20 °C.

Using the optimized condition, we investigate the substrate scope of the reaction (Scheme 2). Different substituted R^1 at the α-position of dihydrocoumarins, including allylic, propargylic, ester, and benzylic moieties, were investigated, and we found that the pentanidium **P4**-catalyzed reactions were able to provide the corresponding alkylated products **2b**−**2i** in good yields and enantioselectivities (Scheme 2). We also found that different electrophiles including allylic and benzyl bromide bearing either electron-donating or electron-withdrawing groups could also be successfully used as electrophiles to give products **2j**−**2r**. Different substituents R^2 on the aromatic ring of dihydrocoumarins have limited effect on stereoselectivity leading to useful results (**2s**−**2w**). Both 3,4-dihydro-2*H*-benzo[h]chromen-2-one **2x** and 1,2-dihydro-3*H*-benzo[f] chromen-3-one **2y**−**2ac** are also viable substrates for this methodology. These compounds should appeal to those interested in posttranslational modification of histones as splitomicin (parent compound of **2y**) and analogues have been shown to be potent inhibitors of Sir2 proteins.[8]

Enantioselective Alkylation of Cyclic and Linear Ketones. Seminal work by Dolling[12a] on the enantioselective methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone left an inaccurate impression that asymmetric alkylation of cyclic ketones can be achieved with ease.[12] On the contrary, there is an absence of suitable phase transfer catalyst for highly enantioselective direct alkylation of both simple cyclic ketones and fused cyclic ketones. Innovative solution of this problem by

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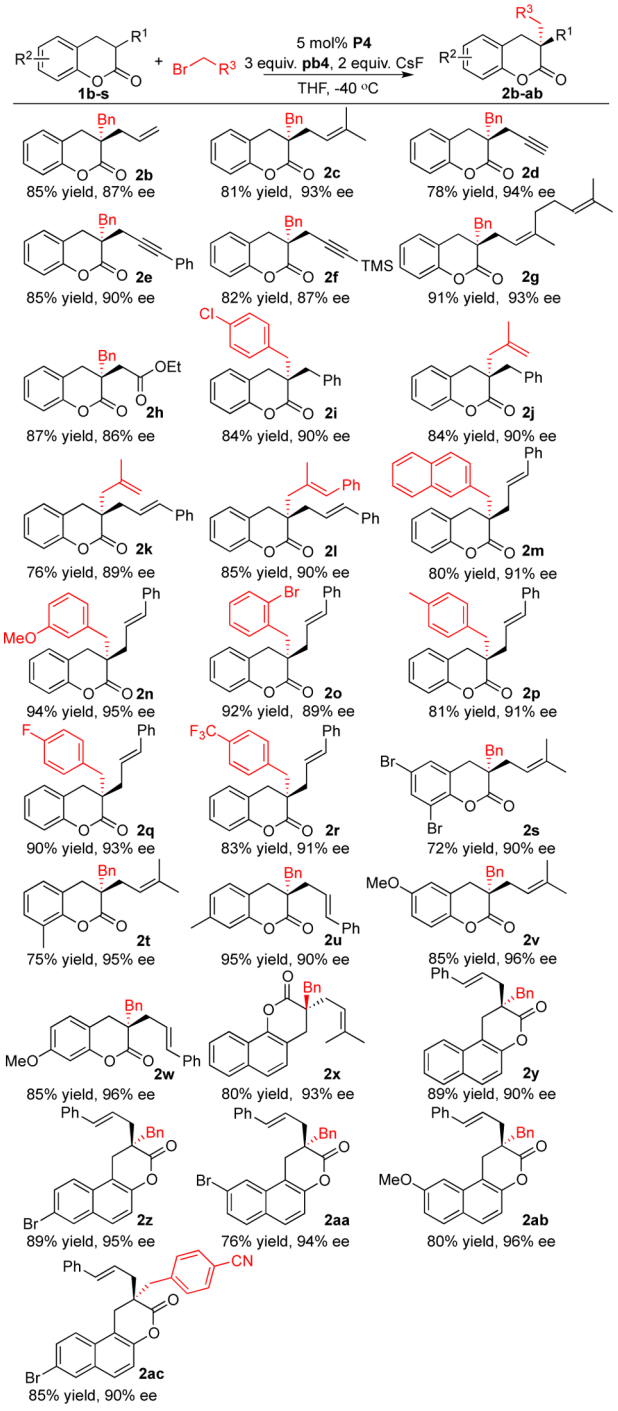
Scheme 2. Pentanidium-Catalyzed Enantioselective Alkylation of Dihydrocoumarins and Benzochromenones[a,b]

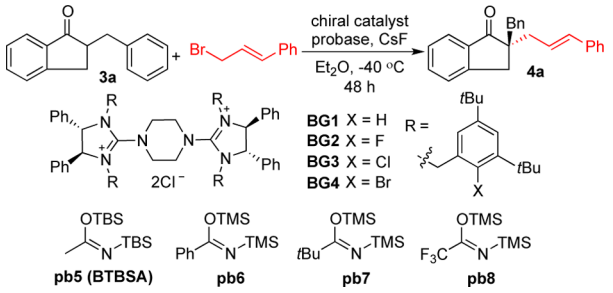


[a]Reactions were carried out with **1** (0.10 mmol), electrophile (0.20 mmol), **pb4** (0.3 mmol), CsF (0.2 mmol), and **P4** (5 mol %) in 0.4 mL of THF at −40 °C for 24 h. [b]Isolated yields, ee was determined by HPLC.

Maruoka et al. includes the use of cyclic β-ketoesters[12e] and 2-arylcyclohexanone modified with a *N*,*N*-diphenylaminomethylene group.[12i] The situation with linear ketones is similarly dire except for α-hydroxyketone.[13]

We found that the optimized condition for the alkylation of dihydrocoumains was not suitable for the cyclic ketones such as α-benzyl-1-indanone **3a** (Table 3, entry 1). We believed that a higher concentration of fluoride source is required to activate the silyl enol ethers, which are more stable than silyl ketene acetal (entry 2). We recently reported that chiral dicationic bisguanidinium, ion-paired with permanganate, catalyzed the asymmetric oxidation reaction of alkenes;[14a] similarly, bisguanidinium diphosphatobisperoxotungstate ion-pair was found to catalyze asymmetric sulfoxidation.[14b] We found that when we use bisguanidiniums **BG1**−**4** (entries 3−6), the profile of the reactions improved for **BG1**−**2**. We investigated several more probases **pb5**−**8** (entries 7−10) and found that the best combination for this reaction is between bisguanidinium **BG1** and **pb5** (BTBSA, bis(*tert*-butyldimethylsilyl)acetamide). These results clearly indicated the role of the probase in determining both the reactivity and enantioselectivity of the reaction.

Table 3. PTC Alkylation of α-Benzyl-1-indanone 3a[a]



entry	catalyst (mol %)	probase (equiv)	CsF (equiv)	yield[b]	ee[c]
1[d]	**P4** (10)	**pb4** (3)	2	trace	–
2	**P4** (10)	**pb4** (2)	5	92	43
3	**BG1** (10)	**pb4** (2)	5	90	80
4	**BG2** (10)	**pb4** (2)	5	88	78
5	**BG3** (10)	**pb4** (2)	5	84	15
6	**BG4** (10)	**pb4** (2)	5	83	13
7	**BG1** (10)	**pb6** (2)	5	94	79
8	**BG1** (10)	**pb7** (2)	5	90	78
9	**BG1** (10)	**pb8** (2)	5	trace	–
10	**BG1** (10)	**pb5** (2)	5	98	95

[a]Reaction was carried out with **3a** (0.10 mmol), bromide (0.20 mmol), CsF (0.5 mmol, 5.0 equiv), and probase (0.2 mmol, 2.0 equiv) in 0.4 mL of Et_2O at −40 °C for 48 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Main product is silyl enol ether **8a**; probase (0.3 mmol, 3.0 equiv), CsF (0.2 mmol, 2.0 equiv).

Using the results from Table 3 as the basis, we explored a variety of α-benzyl-1-indanones and α-benzyl-tetralones (Scheme 3). Particularly interesting are the ortho-, meta-, and para-trifluoromethyl substituted α-benzyl-1-indanones; they provided α-tetrasubstituted-1-indanones **4b**−**d** in high yields and enantioselectivities. Electron-rich heterocyclic rings such as thiophene and furan also gave good results (**4f**−**4g**). Allylic bromide, propargylic bromide, and methyl bromoacetate are suitable electrophiles leading to their corresponding alkylated products with good results (**4h**−**4l**). Substituents R^2 on the 1-indanone did not affect the results (**4m**−**n**). For α-benzyl-tetralones, the reactions are slower and need more time to complete (**4o**−**u**).

When we attempted direct PTC alkylation of linear ketone such as phenyl ethyl ketone, we found that the conditions used previously were unable to promote the reaction (Table 4, entries 1−3; see Supporting Information for details, Table S2). Instead, we found that silyl enol ether **5a** was activated with a mixture of AgF and CsCl in the presence of 10 mol % of **BG1** and gave ketoester **6a** with good level of enantioselectivity

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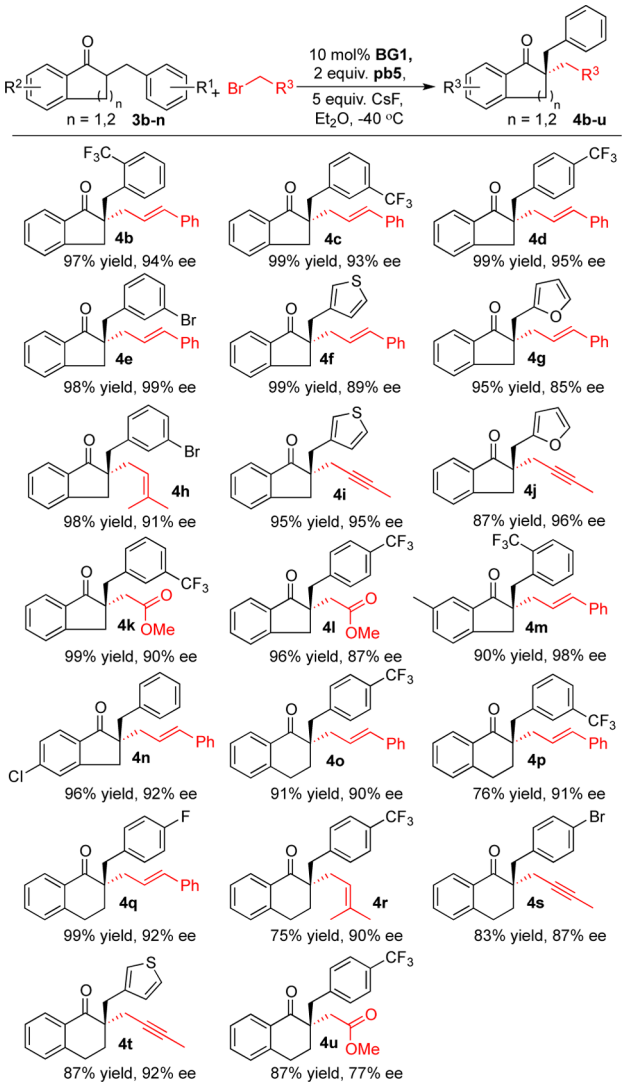
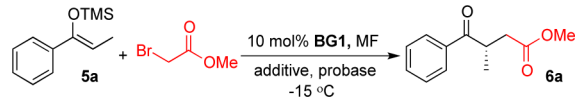
Scheme 3. Bisguanidinium-Catalyzed Enantioselective Alkylation of α-Alkyl-1-indanone and α-Alkyltetralone[a,b,c]



[a]For α-benzyl-1-indanones, reaction was carried out with **3** (0.10 mmol), electrophile (0.20 mmol), **pb5** (0.20 mmol), CsF (0.50 mol), and **BG1** (10 mol %) in 0.4 mL of Et_2O at −40 °C for 72 h. [b]For α-benzyl-tetralones indanone, reaction was carried out for 96 h. [c]Isolated yields; ee was determined by chiral HPLC analysis.

(entries 4−6). With only AgF, the reaction did not proceed (entry 4). We were excited to observe that the reactions can be significantly improved if **pb4** is added to the reaction (entries 7). We found that when amount of probases were reduced to 0.4 equiv, both the yields and enantioselectivities increased (entries 8−9). Extra probase is likely to drive the formation of sily enol ether rather than the productive alkylation reaction pathway. Several alkyl phenyl ketones were investigated, and they were alkylated with methyl 2-bromoacetate with a good level of enantioselectivities (Scheme 4). While ether type solvents (THF, Et_2O) were more suitable for direct alkylation reactions (Scheme 2 and 3), we found that nonpolar solvent such as 4-*tert*-butyltoluene (Scheme 4) can reduce the reaction rate and improve the enantioselectivities significantly for reactions of silyl enol ethers. All absolute configurations were determined by comparing with compounds in the literature (see Supporting Information).

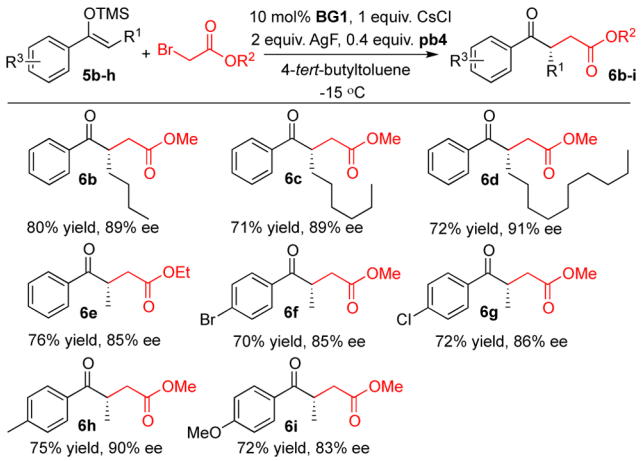
Table 4. PTC Alkylation of Silyl Enol Ether 5a



entry	probase (equiv)	MF (equiv)	additive (equiv)	yield[a]	ee[b]
1	none	CsF (5)	none	50	46
2	**pb4** (0.4)	CsF (2)	none	78	54
3	**pb5** (0.4)	CsF (2)	none	74	49
4	none	AgF (5)	none	trace	–
5	none	AgF (5)	CsCl (1)	47	80
6	none	AgF (2)	CsCl (1)	45	77
7	**pb4** (1)	AgF (2)	CsCl (1)	23	54
8[c]	**pb4** (0.4)	AgF (2)	CsCl (1)	82	86
9[c]	**pb5** (0.4)	AgF (2)	CsCl (1)	80	79

[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]Reaction was carried out with **5a** (0.10 mmol), methyl 2-bromoacetate (0.20 mmol), catalyst (10 mol %), AgF (0.2 mmol, 2.o equiv), probase (0.04 mmol, 0.4 equiv), and CsCl (0.1 mmol, 1.0 equiv) in 0.4 mL of 4-*tert*-butyltoluene for 24 h at −15 °C.

Scheme 4. Bisguanidinium-Catalyzed Enantioselective Alkylation of Silyl Enol Ether 5[a,b]



[a]Reaction was carried out with **5** (0.10 mmol), alkyl 2-bromoacetate (0.20 mmol), **pb4** (0.04 mmol), CsCl (0.10 mmol), and **BG1** (10 mol %) in 0.4 mL of 4-*tert*-butyltoluene for 24 h at −15 °C. [b]Isolated yields; ee was determined by HPLC analysis.

Silyl Ketene Acetal and Silyl Enol Ether as Key Intermediates. Bis(trimethylsilyl)acetamide **pb4** (BSA) is typically used as a silylation reagent,[15a] and it can be used to generate silyl ketene acetal in situ for rearrangement reactions.[15b−f] Silyl ketene acetal **7** was identified via crude NMR to be an intermediate in pentanidium-catalyzed enantioselective alkylation of dihydrocoumarin **1a** (Scheme 5). In order to ascertain the role of the intermediate, dihydrocoumarin **1a** was treated with LiHMDS and TMSCl to prepare silyl ketene acetal **7**. In the presence of 5 mol % of pentanidium **P4** and CsF, enantioselectivitiy of the alkylated adduct **2a** obtained using **7** is similar to the condition using probase and directly with **1a**. This result gives a strong indication that the role of BSA **pb4** is not merely a base but is also responsible for generating silyl ketene acetal **7**, which is an important intermediate in the reaction.

We found that with direct alkylation of α-benzyl-1-indanone **3a** using bisguanidinium **BG1** as catalyst and in the presence of

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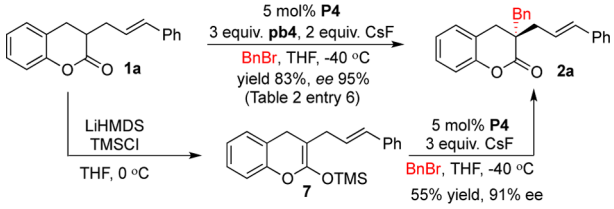
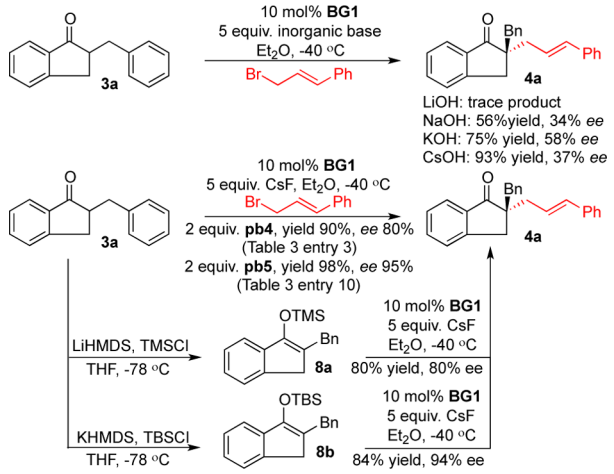
Scheme 5. Silyl Ketene Acetal as an Intermediate for Enantioselective Alkylation of Dihydrocoumarin 1a



inorganic hydroxides, moderate levels of enantioselectivities were observed (Scheme 6; see Supporting Information for

Scheme 6. Silyl Enol Ether as an Intermediate for Enantioselective Alkylation of α-Benzyl-1-indanone 3a



details, Table S3). We also found that probase BTBSA **pb5** provided alkylated product with higher level of enantioselectivities compared with BSA **pb4**, when they are use in the presence of **BG1** for the alkylation reactions of **3a** (Table 3, entries 3 and 10). Similar to the dihydrocoumarins (Scheme 5), we suspect that silyl enol ether intermediates are key intermediates in these reactions with α-benzyl-1-indanone **3a**. We prepared TMS enol ether **8a** and TBS enol ether **8b** from α-benzyl-1-indanone **3a**. Silyl enol ethers **8a** and **8b** were independently submitted to the alkylation condition in the absence of **pb4** and **pb5**, respectively (Scheme 6). The enantioselectivities obtained were in line with the conditions with probase albeit with slightly lower yields. These observations lead us to the conclusion that there are two roles for the probase—as a base to generate enolate from the ketone and maintaining silyl enol ether as an intermediate in the reaction.

We thus propose a working model that includes these two key roles (Figure 2). The probase is activated with fluoride to provide a chiral organic base, which is an ion-pair between chiral bisguanidinium cation and silylamide.[16] The silylamide removes the α-proton from α-benzyl-1-indanone to generate an enolate **A**, and silyl enol ether **B** is subsequently formed. Further fluoride action results in hypervalent silicates **C** and **D**.[17] From this point, there are two possible pathways. The first involves the release of silylfluoride and the formation of the "naked" enolate.[18] The enolate forms a complex with bisguanidium, and the alkylation proceeds through this complex. Alternatively, bisguanidinium silicate ion-pairs **C** and

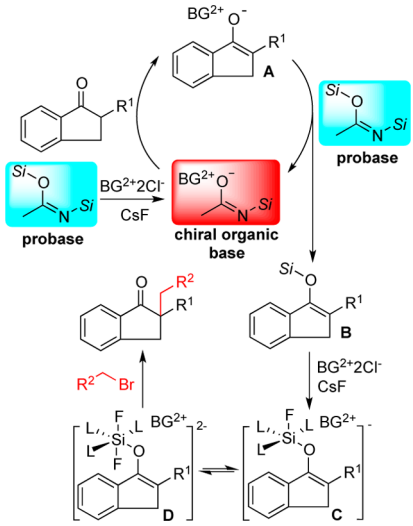


Figure 2. Working model for enantioselective alkylation using silylamide as probase.

D are formed, and they determine the selective enantiofacial approach of the electrophiles. The later proposal concurs better with the observation that similar probases **pb4** (TMS) and **pb5** (TBS), except for difference in their steric features, gave different levels of enantioselectivities (Scheme 6). Similarly, different probases **pb4** (TMS), **pb6** (TMS), and **pb7** (TMS) but with the same silyl group gave the same level of enantioselectivities (Table 3, entries 3, 7, and 8). The requirement for an excess of fluoride source is also consistent with this proposal. While the use of quaternary ammonium fluoride for the activation of silyl enol ether for enantioselective Mukaiyama-type aldol reactions is known, it has not been very successful.[19] There is also an absent of methods using silyl enol ether in the presence of chiral quaternary ammonium fluoride for enantioselective alkylation reactions. The gap is now filled using with this current methodology using bis(trimethylsilyl)-acetamide **pb4** (BSA) and bis(*tert*-butyldimethylsilyl)acetamide **pb5** (BTBSA) as both probase and silylation reagent.

CONCLUSIONS

We have demonstrated a Brønsted probase strategy, which generates a strong base in situ through the use of a silylamide and fluoride. While both probase and CsF are used in excess, the active chiral organic base is present in only substoichiometic amount not greater than the amount of the chiral cations. Otherwise, high levels of enantioselectivities will not be observed. This approach was successfully for the enantioselective alkylation of dihydrocoumarins, cyclic and linear ketones. We found that silyl enol ether and silyl ketene acetal are key intermediates in these reactions. We propose that the formation of pentanidium and bisguanidinium silicate ion-pairs are important for the selective enantiofacial approach of the electrophiles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05053.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Calculations predict that O-TMS cleavage of BSA by CsF has a barrier of 11.9 kcal/mol, which is substantially lower than the barrier for N-TMS cleavage (20.7 kcal/mol). Thus, it is proposed that O-TMS of BSA would be preferentially cleaved over N-TMS. See Supporting Information for details.

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