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Organocatalytic asymmetric Michael reaction with acylsilane donors†

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We have developed an organocatalytic asymmetric Michael reaction of acylsilane through the selection of acylsilane substrates and organocatalysts, thus creating a rare example of acylsilane α-alkylation with a chiral guanidine catalyst, which afforded products in good yields and high stereoselectivity. The corresponding adducts described here have also been demonstrated to be useful in the synthesis of unnatural amino acids and biologically active compounds.

Introduction

Since their discovery by Brook in 1957,[1–3] acylsilanes have been the one of the most powerful and efficient compounds that have the silicon directly attached to the carbonyl group, exhibiting particular physical and chemical properties,[4–8] so that they can be easily transformed into many different derivatives in one pot, such as acid,[9–12] ketone,[13–15] alcohol,[16,17] aldehyde,[11,18,19] cyanogen,[20] amide[12,20,21] and ester.[20,22] In addition to these radical reactions, a great deal of effort has been devoted to the development of various other kinds of acylsilane reactions, for instance, stereocontrolled nucleophilic additions,[23] stereocontrolled aldol reactions,[24] cyclization,[25] coupling reaction,[26] α-halogenations,[3] and enantioselective reduction.[27]

However, due to their slightly higher pK_a values (the values being approximately 16)[28] compared with ketones, aldehydes, and 1,3-dicarbonyl substrates, the α-alkylation of acylsilanes is more difficult. In addition, more challenges still remain regarding substrate scope and reaction selectivity, including diastereo- and enantioselectivity. More recently, Xue-Long Hou and co-workers have described the palladium-catalyzed allylic alkylation of acylsilanes with monosubstituted allyl substrates, which can afford high ee and moderate dr ratio.[29] Despite these creative efforts, the direct α-alkylation of acylsilanes induced by the deprotonation of its α position by chiral base remains a considerable challenge. For this reason, acylsilanes with hydrogen atoms on the alpha position were applied in this study as nucleophile to obtain chiral α-alkylated product (Fig. 1).

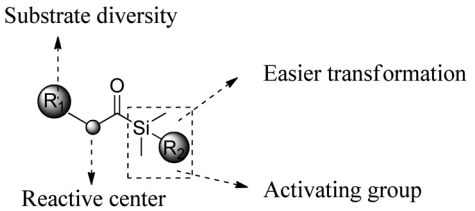

Fig. 1 Structure of nucleophile acylsilanes.

As we know, Michael reactions are among the most powerful and efficient methods for carbon–carbon bond formation. In particular, the development of organocatalytic asymmetric Michael reactions of carbonyl compounds with nitroalkenes has garnered great interest in recent years.[30–34] However, asymmetric Michael reactions using monoester or acid directly as prenucleophiles have never been reported. The use of pyrazole amides as special Michael donors to react with nitroolefins, reported by Barbas III and co-workers, and the use of quinine derived urea catalysts gave the desired product with high dr and ee value.[35] However, most of the good results for these reactions are limited to Michael donor substrates with an electron-withdrawing aromatic group. Herein, we describe a new organocatalyzed asymmetric Michael reaction using acylsilanes as donors to afford diverse and structurally complex α-alkyl acylsilanes with high diastereo- and enantioselectivity.

Due to the versatile properties of acylsilanes, the use of acylsilanes as promising Michael donors is meaningful. However, this poses a distinct and formidable challenge: the slightly lower pK_a values of acylsilanes limited the catalyst selection.[28] Chiral guanidines, because of the characteristics of high pK_a values and hydrogen-bonding activation, have been shown to be efficient catalysts for enantioselective reactions.[36–39]

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†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic and analytical data for all compounds, mechanism evidence and the determination of absolute configuration for Michael adducts. See DOI: 10.1039/c2ob26950c

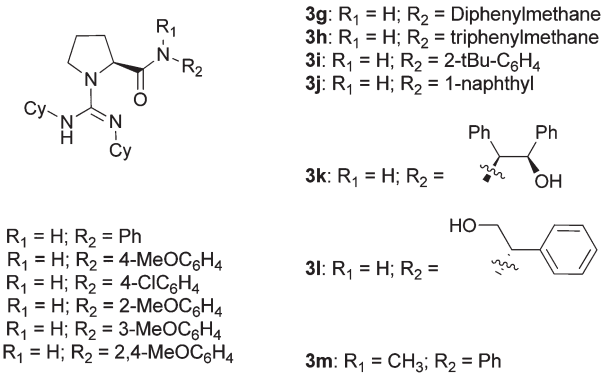


Fig. 2 Chiral guanidines applied in this study.

Recently, the Xiaoming Feng group has described several asymmetric reactions which were catalyzed by bifunctional guanidine catalysts.[40–44] Intrigued by these challenges and advantages, we have pursued a chiral guanidine catalyzed enantioselective Michael reaction, using acylsilanes and nitroolefins as substrates.

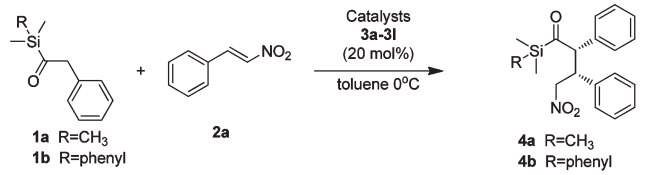
Results and discussion

We initiated our studies by evaluating a template Michael reaction with acylsilane **1a** and nitroolefin **2a** in the presence of different kinds of catalysts. As we expected, most of chiral organobases, such as cinchonine or quinine, couldn't catalyze this reaction (see ESI,† Table S1). However, the reaction catalyzed by chiral guanidine **3a** derived from prolinamide (Fig. 2) proceeded smoothly and afforded the desired product in 40% yield with excellent diastereoselectivity (99 : 1 dr) and moderate enantioselectivity (76% ee) (Table 1, entry 1). Therefore, more chiral guanidines have been synthesized and evaluated (**3b–3l**, Fig. 2).

The results showed that catalysts containing electron donating groups on the phenyl group of the amide domain gave higher enantioselectivity (Table 1, entries 1–3). However, attempts to optimize the reaction by then conducting it with other catalysts bearing electron donating groups at a different position of the phenyl group failed to provide the desired improvements in chemical and optical yield (Table 1, entries 4–6). Further examinations were focused on the sterically hindered amide subunit backbones.

The results suggested that the amide subunit in the guanidine had a significant impact on the enantioselectivity of the reaction.[45] Catalyst **3g** with diphenylmethanamine backbone gives the best result with 99 : 1 dr and 91% ee (Table 1, entries 7–9). We have tried to improve the catalytic result through introducing more hydrogen bond donors into chiral guanidine catalysts (**3k**, **3l**). Unfortunately, the expected improvement of reaction result was not found (Table 1, entries 11–12). The substitution of the trimethylsilyl group with a dimethylphenylsilyl group on the acylsilane gives a higher yield (81%) with slightly lower dr (16 : 1) and similar ee value (91%) (Table 1, entry 13).

Table 1 Optimization of the reaction catalyst[a]



Entry	Cat.	Acylsilane	Yield[b] [%]	*syn* : *anti*[c]	ee[c] [%]
1	**3a**	**1a**	47	>99 : 1	76
2	**3b**	**1a**	46	>99 : 1	81
3	**3c**	**1a**	37	>99 : 1	64
4	**3d**	**1a**	35	>99 : 1	73
5	**3e**	**1a**	42	>99 : 1	73
6	**3f**	**1a**	55	>99 : 1	68
7	**3g**	**1a**	43	>99 : 1	91
8	**3h**	**1a**	34	>99 : 1	76
9	**3i**	**1a**	52	>99 : 1	89
10	**3j**	**1a**	39	>99 : 1	37
11	**3k**	**1a**	42	>99 : 1	62
12	**3l**	**1a**	47	>99 : 1	78
13	**3g**	**1b**	**81**	**16 : 1**	**91**

[a] Unless otherwise noted, the reaction was carried out with 0.10 mmol acylsilane, 0.25 mmol nitroolefin and 20 mol% guanidine catalyst in toluene (1.5 mL) at 0 °C for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC.

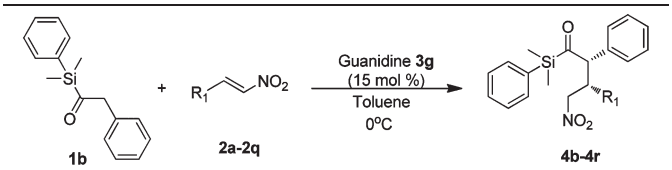
In addition, it is noteworthy that **1a** was more difficult to synthesize compared with **1b** (see ESI,† Scheme S1). Therefore, we explored the scope of the chiral guanidine catalyst **3g** with dimethylphenyl acylsilane as the substrate.

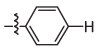
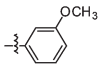
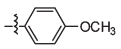
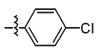
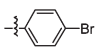
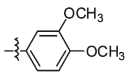
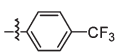
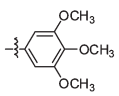
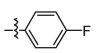
Under the optimized conditions (see ESI,† Table 2), various nitroolefin substrates were investigated to afford a wide range of products **4** containing two chiral centers with good diastereomeric ratios (>10 : 1 dr) and high ee values (89–96% ee), which is illustrated in Table 2. It is interesting to note that for the use of β-aryl nitroolefins, the position and the electronic properties of the substituents on the aromatic ring appeared to have a very limited effect on the stereoselectivity (Table 2, entries 1–14).

Regardless of the type of substituent on the aromatic ring, be them electron-withdrawing (Table 2, entries 7–10, 12 and 14), electron-donating (Table 2, entries 2–6, 11, 13), or neutral (Table 2, entry 1) or the substitution pattern (*para*, *meta*, or *ortho*; Table 2, entries 2–10), the reactions of these nitroolefins with acylsilane gave the desired product in good yield and selectivity. The substrates with condensed-ring (Table 2, entry 15) or hetero aromatic groups (Table 2, entry 16) furnished the desired product with high diastereoselectivity and enantioselectivity. The reaction also worked well for the alkyl-nitroolefin, affording an 85% yield of product with a 12 : 1 *syn*–*anti* ratio and a 90% ee value under the optimized reaction conditions (Table 2, entry 17).

Further explorations were focused on the generality of the reaction with regards to variation of the dimethylphenyl acylsilane substrate under the same optimized conditions. It is noteworthy that the electronic properties and steric effects of the aromatic ring substituents on the acylsilane had no obvious

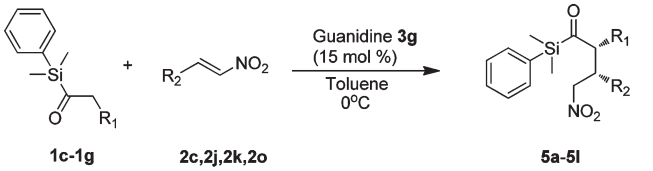
Table 2 Generality of reaction demonstrated with a variety of nitroolefin electrophiles[a]

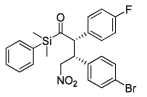
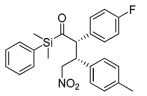
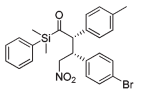
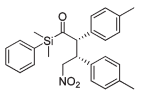
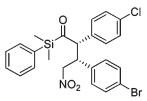
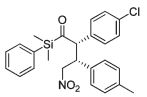
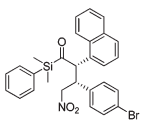
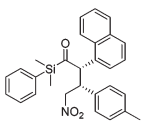
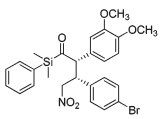
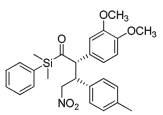
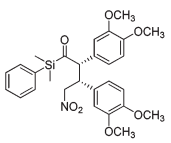
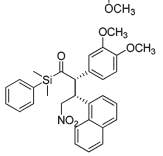


Entry	R_1	Yield[b] [%]	*syn* : *anti*[c]	ee[c] [%]
1		**4b**, 86	16 : 1	91
2		**4c**, 78	27 : 1	92
3		**4d**, 84	80 : 1	93
4		**4e**, 81	>99 : 1	91
5		**4f**, 77	52 : 1	93
6		**4g**, 85	17 : 1	90
7		**4h**, 75	19 : 1	93
8		**4i**, 61	82 : 1	91
9		**4j**, 78	49 : 1	93
10		**4k**, 77	>99 : 1	96
11		**4l**, 83	45 : 1[d]	94
12		**4m**, 76	44 : 1	93
13		**4n**, 79	>99 : 1	93
14		**4o**, 86	99 : 1	91
15		**4p**, 84	>99 : 1[d]	93
16		**4q**, 75	25 : 1	89
17		**4r**, 85	12 : 1	90

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol acylsilane, 15 mol% **3g** and 60 mg 4 Å molecular sieves in toluene (1.5 mL) at 0 °C for 12 h, and 0.25 mmol nitroolefin dissolved in toluene was added to the mixture in 4 portions over 8 h (see ESI,† Scheme S4). [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR.

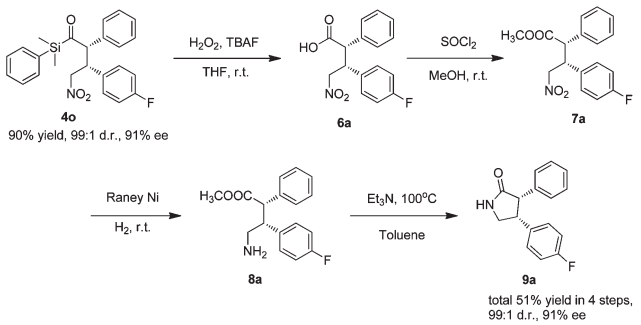
Table 3 Generality of the reaction with respect to the acylsilane derivative[a]



Entry	R_1	Yield[b] [%]	*syn*/*anti*[c]	ee[c] [%]
1		**5a**, 81	>99 : 1	92
2		**5b**, 78	24 : 1	95
3		**5c**, 75	25 : 1	92
4		**5d**, 82	98 : 1	92
5		**5e**, 87	>99 : 1[d]	90
6		**5f**, 85	99 : 1	93
7		**5g**, 51	>99 : 1[d]	94
8		**5h**, 71	>99 : 1	97
9		**5i**, 77	35 : 1	95
10		**5j**, 82	>99 : 1	94
11		**5k**, 76	>99 : 1[d]	93
12		**5l**, 81	44 : 1	96

[a] The reaction was carried out with 0.1 mmol acylsilane, 15 mol% **3g** and 60 mg 4 Å molecular sieves in toluene (1.5 mL) at 0 °C for 12 h, and 0.25 mmol nitroolefin dissolved in toluene was added to the mixture partially in 4 time over 8 h (see ESI,† Scheme S4). [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR.

influence on the reactivity and stereoselectivity of the guanidine **3g** catalyzed Michael reaction (Table 3). All the aryl acylsilanes with electron-withdrawing (Table 3, entries 1, 2, 5, 6) or electron-donating groups (Table 3, entries 3, 4, 9–12) or condensed-rings (Table 3, entries 7, 8) gave the desired products



Scheme 1 Synthesis of an activated chiral medicine intermediate.

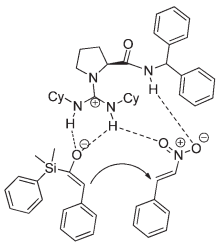


Fig. 3 The proposed dual-activation mode[40] of guanidine **3g** catalyzed Michael reaction between acylsilane and nitroolefin.

with high diastereoselectivity and enantioselectivity. However, derivatives of acylsilane with alkyl groups in place of an aromatic ring were virtually unreactive under the model reaction conditions (data not shown), thus suggesting that an aromatic functionality is required to bring the pK_a value into a functional range for these organocatalytic conditions.

In addition, Michael addition of acylsilanes to nitroolefins is an efficient synthetic tool for the construction of other functionalized compounds. For example, γ amino acids could be obtained in two steps with high yield without changes in diastereo- and enantioselectivity (see ESI,† Scheme S5). On account of the high efficiency in this organocatalysis of the Michael adducts, the reaction was carried out on a 2 g scale in the presence of **2g** (15 mol%) with the substrates (**1b** and **2n**) and gave the desired product **4o** in 90% yield and with 99 : 1 dr and 91% ee. **4o** was successfully converted exclusively into the corresponding carboxylic acid in good yield under oxidization conditions.[10] Further reaction of the **6a** with $SOCl_2$ in methanol to afforded ester **7a**, which was then reduced in the presence of RANEY® Ni and H_2 to obtain **8a**. Cyclization of **8a** was carried out in toluene with Et_3N to furnish target **9a** in 51% total yield for 4 steps of reactions without any loss of stereoselectivity (Scheme 1). The final chiral product, 2-pyrolidinone **9a**, possesses great potential in pharmaceutical applications;[46] it is active on the central nervous system, and in particular it has valuable anxiolytic and antidepressive properties.

To explore the mechanism of the guanidine catalyzed Michael reaction, comparative experiments were carried out with the N-Me derivative (**3m**) (see ESI,† Scheme S7) of the corresponding guanidine catalyst **3a**. The enantioselectivity decreased dramatically from 76% ee (Table 1, entry 1) to 28% ee (see ESI,† Scheme S8) under the same reaction conditions. Therefore, our findings, together with the dual activation model proposed by the group of Feng and co-workers suggest that the nitroolefin and the acylsilane substrates, might be activated simultaneously by the catalyst (Fig. 2), and the NH proton of the amide moiety is vital for the high activity and enantioselectivity. As illustrated in Fig. 3, the guanidine moiety of the catalyst likely functions as a base, thus enabling intracomplex deprotonation, while the N–H moiety of the amide in the catalyst might act as a Brønsted acid[47] to activate the Michael acceptor. This plausible TS leads to mostly *syn* products. The absolute configuration of **4b** was determined by comparing the NMR and chiral HPLC spectra of the derivative of **4b** with that of literature data (see ESI,† Scheme S9) and is in accordance with the configuration predicted by this model.

Conclusions

In conclusion, we have developed an organocatalytic asymmetric Michael reaction of acylsilane through the selection of acylsilane substrate and organocatalyst, thus creating a rare example of acylsilane α-alkylation with a chiral guanidine catalyst, which afforded products in good yields and high stereoselectivity, regardless of the type of substituent on the aromatic rings of the acylsilane or nitroolefin substrates. The described straightforward process to afford the corresponding adducts under mild reaction conditions has also been demonstrated to be useful in the synthesis of unnatural amino acids and biologically active compounds. This class of novel acylsilane substrate as a pronucleophile should facilitate the development of a wide range of asymmetric reactions that can be catalyzed by organic and metal catalysts; some of these reactions have already been realized in our group and will be reported in the near future.

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