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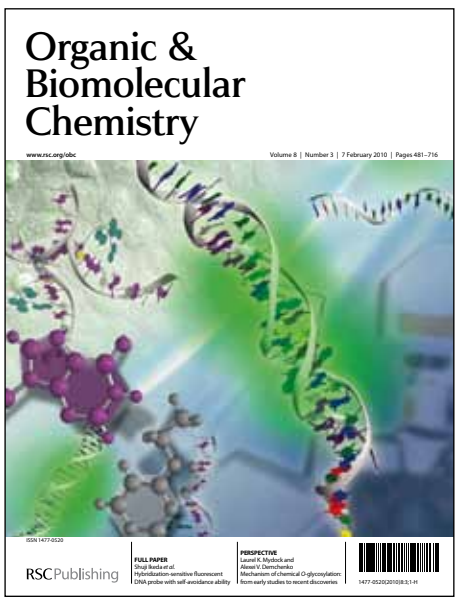

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Organocatalytic Asymmetric Michael Reaction with Acylsilanes Donors†

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We have developed an organocatalytic asymmetric Michael reaction of acylsilane through the selection of acylsilane substrates and organocatalyst, thus creating a rare example of acylsilanes α-alkylation with 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 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 could be easily transformed into many different derivatives in one spot, such as acid[9-12] , ketone[13-15], alcohol[16, 17], aldehyde[11, 18, 19], cyanogens[20], amide[12, 20, 21] and ester [20, 22]. Beside of these radical reaction, a great deal of effort has been devoted to the development of various kinds of reactions acylsilanes participated, Involving stereocontrolled nucleophilic additions[23], stereocontrolled aldol reactions[24], cyclization[25], coupling reaction[26], α-halogenations[3], Enantioselective reduction[27].

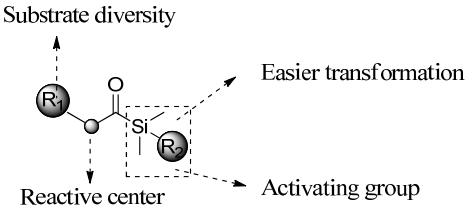
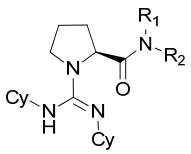
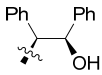


Fig. 1. Structure of nucleophile acylsilanes

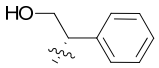
However, due to the slightly higher pK_a values (the values being approximately 16)[28] compared with ketones, aldehydes, and 1,3-dicarbonyl substrates, the α-alkylation of acylsilanes is more difficult. In addition, more challenges still remain regarding substrate scope and reaction selectivity, including 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 middle dr ratio[29]. Despite these creative efforts, the direct α-alkylation of acylsilanes induced by the deprotonation of it's alpha position by chiral base remains a considerable challenge. For this reason, acylsilanes with hydrogen atoms on the alpha position was applied in this study as nucleophile to obtain chiral α-alkylated product (Fig. 1).



3g: R_1 = H; R_2 = Diphenylmethane
3h: R_1 = H; R_2 = triphenylmethane
3i: R_1 = H; R_2 = 2-tBu-C_6H_4
3j: R_1 = H; R_2 = 1-naphthyl

3k: R_1 = H; R_2 = 

3a: R_1 = H; R_2 = Ph
3b: R_1 = H; R_2 = 4-$MeOC_6H_4$
3c: R_1 = H; R_2 = H; R_2 = 4-ClC_6H_4
3d: R_1 = H; R_2 = 2-$MeOC_6H_4$
3e: R_1 = H; R_2 = 3-$MeOC_6H_4$
3f: R_1 = H; R_2 = 2,4-$MeOC_6H_4$

3l: R_1 = H; R_2 = 

3m: R_1 = CH_3; R_2 = Ph

Fig. 2 Chiral guanidines applied in this study.

As we know, Michael reactions are among the most powerful and efficient methods for carbon-carbon bond formation. Particularly, 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 reported. The use of pyrazole amide as special Michael donors to react with nitro olefins, 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 good results for these reactions are limited to Michael donors substrates with electron-withdrawing aromatic. Herein, we describe a new organocatalyzed asymmetric Michael reaction by using acylsilane as donor to afford diverse and structurally complex α-alkyl acylsilanes with high diastereo- and

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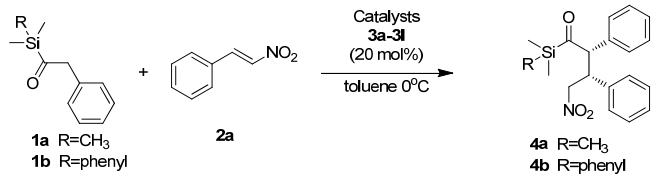
†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic and analytical data for all compounds, Mechanism evidence and the determination of absolute configuration for Michael adducts. See DOI: 10.1039/XXXXXXXXX

enantioselectivity.

Due to the versatile property 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]. Recently, Xiaoming Feng group has described serveral asymmetric reactions which was 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 nitro olefins as substrates.

Results and discussion

Table 1. Optimization of the reaction catalysts[a]



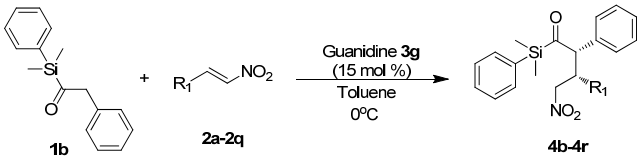
Entry	Cat.	Acylsilane	Yield[%][b]	Syn/anti[c]	ee[%][c]
1	**3a**	**1a**	47	>99:1	76
2	**3b**	**1a**	46	>99:1	81
3	**3c**	**1a**	37	>99:1	64
4	**3d**	**1a**	35	>99:1	73
5	**3e**	**1a**	42	>99:1	73
6	**3f**	**1a**	55	>99:1	68
7	**3g**	**1a**	43	>99:1	91
8	**3h**	**1a**	34	>99:1	76
9	**3i**	**1a**	52	>99:1	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**

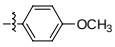
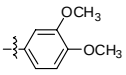
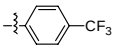
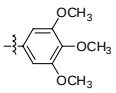
[a] Unless otherwise noted, the reaction was carried out with 0.10 mmol acylsilane, 0.25 mmol nitroolefin and 20 mol% guanidine catalyst in toluene (1.5 mL) at 0℃ for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC.

We initiated our studies by evaluating 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 catalyzed 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).

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

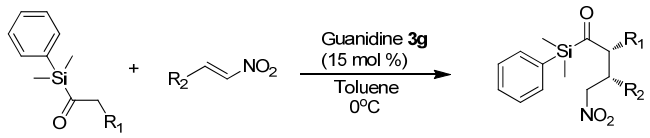
Table 2. Generality of reaction demonstrated with a variety of nitroolefins electrophiles[a]



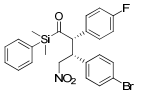
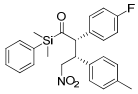
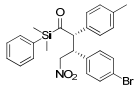
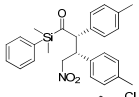
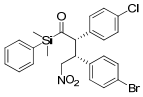
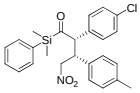
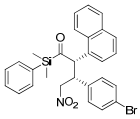
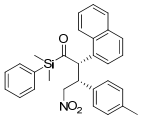
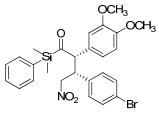
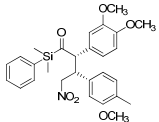
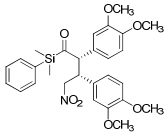
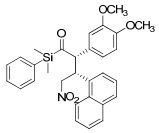
Entry	R_1	Yield[%][b]	Syn/anti[c]	ee[%][c]
1		**4b**, 86	16:1	91
2		**4c**, 78	27:1	92
3		**4d**, 84	80:1	93
4		**4e**, 81	>99:1	91
5		**4f**, 77	52:1	93
6		**4g**, 85	17:1	90
7		**4h**, 75	19:1	93
8		**4i**, 61	82:1	91
9		**4j**, 78	49:1	93
10		**4k**, 77	>99:1	96
11		**4l**, 83	45:1[d]	94
12		**4m**, 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, 15mol % **3g** and 60 mg 4A molecular sieve in toluene (1.5 mL) at 0℃ 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.

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



1c-1g 2c,2j,2k,2o 5a-5l

Entry	R1	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, 15mol % **3g** and 60 mg 4A molecular sieve in toluene (1.5 mL) at 0℃ 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.

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, entry 7-9). We have tried to improve the catalytic result through introducing more hydrogen bond donors into chiral guanidine catalysts (**3k**, **3l**). Unfortunately, expected improvement of reaction result can't be found (Table 1, entry 11-12). The substitution of trimethylsilyl group with dimethylphenyl silyl group on acylsilane gaves higher yield (81%) with slightly lower dr (16:1) and similar ee value (91%) (Table 1, entry 13,). In addition, it is noteworthy that **1a** was more difficult to synthesize comparing with **1b** (See ESI†, Scheme S1). Therefore, we explored the scope of the chiral guanidine catalyst **3g** with dimethylphenyl acylsilane as the substrate.

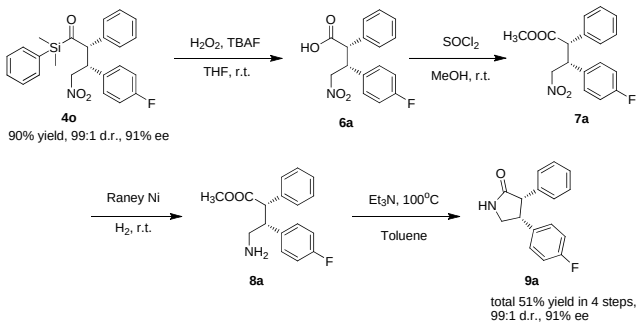
Under the optimized conditions (See ESI†, Table 2), various nitroolefin substrates were investigated to afford a wide range of products **4** containing two chiral centers with good diastereomeric ratios (>10:1 dr) and high ee values (89-96% ee), which was illustrated in Table 2 . It is interesting to 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 stereoselectivity (Table 2, entry 1-14,).

Regardless of the type of substituents on the aromatic rings, be them electron-withdrawing (Table 2, entry 7-10, 12 and 14), electron -donating (Table 2, entry 2-6, 11, 13), or the neutral (Table 2, entry 1) or the substitution pattern (para, meta, or ortho; Table 2, entry 2-10), the reactions of these nitro olefins with acylsilane gave the desired product in good yield and selectivity. The substrates with condensed-ring (Table 3, entry 15) or hetero aromatic groups (Table 2, entry 16) furnished the desired product with high diastereoselectivity and enatioselectivity. 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 substrates under the same optimized condition. It is noteworthy that the electronic properties and steric effects of the aromatic ring substituents on acylsilane had no obvious influences on the reactivities and stereoselectivity of guanidine **3g** catalyzed Michael reaction (Table 3). All the aryl acylsilanes with electron- withdrawing (Table 3, entry 1, 2, 5, 6), electron -donating groups (Table 3, entry 3, 4, 9-12) or condensed-ring (Table 3, entry 7, 8) gave the desired products with high diastereoselectivity and enatioselectivity. However, derivatives of acylsilane with alkyl groups in place of an aromatic ring was 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 potential 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 condition[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 application[46] which is active on the central nervous system, in particular it has valuable anxiolytic and antidepressive properties.



Scheme 1 Synthesis routes of activated chiral medicine intermediate.

To explore the mechanism of the guanidine catatlyzed Michael reaction, comparative experiments were carried out with the N-Me derivative (**3m**) (See ESI†, Scheme S7) of corresponding guanidine catalyst **3a**. The enatioselectivity decreased dramatically from 76% ee (Table 1, entry 1) to 28% ee (See ESI†, Scheme S8) under the same reaction condition. Therefore, our findings, together with the dual activation model proposed by the group of Feng and co-workers suggest that the nitro olefin and the acylsilane substrates, might be activated simultaneously by the catalyst (Fig. 2), and NH proton of the amide moiety is vital for the high activity and enantioselectivity. Just as illustration in (Fig. 3), the guanidine moiety of the catalyst likely functions as a base, thus enabling intracomplex deprotonation, while N-H moiety of the amide in 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 it is in accordance with the configuration predicted by this model.

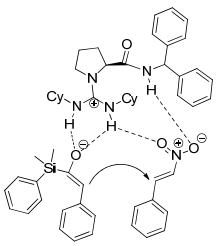


Fig. 3 The proposed dual-activation mode[20a] of guanidine **3g** catalyzed Michael reaction between acylsilane and nitroolefin.

Conclusions

In conclusion, we have developed an organocatalytic asymmetric Michael reaction of acylsilane through the selection of acylsilane substrates and organocatalyst, thus creating a rare example of acylsilanes α-alkylation with chiral guanidine catalyst, which afforded products in good yields and high stereoselectivity, regardless of the type of substituents on the aromatic rings of acylsilane or nitro olefin substrates. The described straightforward process to afford the corresponding adducts under mild reaction conditions has also been demonstrated to be useful in synthesis of unnatural amino acids and biologically active compounds. This class of novel acylsilane substrate as a pronucleophile should facilite 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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