

A Catalyst Designed for the Enantioselective Construction of Methyl- and Alkyl-Substituted Tertiary Stereocenters

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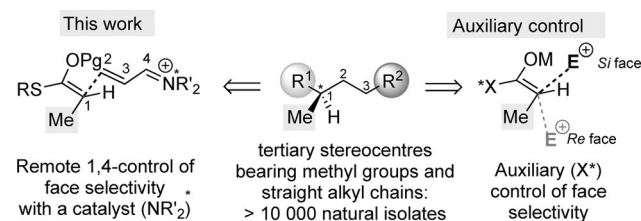
Abstract: Tertiary methyl-substituted stereocenters are present in numerous biologically active natural products. Reported herein is a catalytic enantioselective method for accessing these chiral building blocks using the Mukaiyama–Michael reaction between silyl ketene thioacetals and acrolein. To enable remote enantioface control on the nucleophile, a new iminium catalyst, optimized by three-parameter tuning and by identifying substituent effects on enantioselectivity, was designed. The catalytic process allows rapid access to chiral thioesters, amides, aldehydes, and ketones bearing an α -methyl stereocenter with excellent enantioselectivities, and allowed rapid access to the C4–C13 segment of (–)-bistramide A. DFT calculations rationalized the observed sense and level of enantioselectivity.

Tertiary stereocenters bearing either methyl, ethyl, or other simple alkyl groups are present in numerous biologically active natural products, such as in polyketides and terpenoids. Over 10 000 known natural products bear structural subunits of this type.^[1] Very often, such stereocenters are found adjacent to a linear chain of methylene (CH_2) groups (Scheme 1 a). The conformational flexibility of the methylene chains usually prevents the induction of stereochemistry from remote positions.^[2]

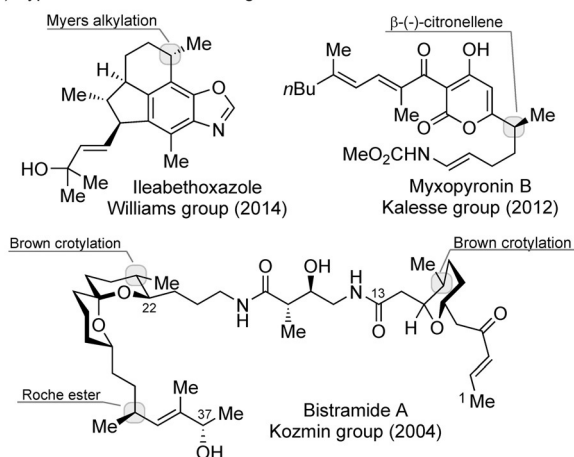
In the total synthesis of natural products and synthesis of pharmaceuticals, these methyl-bearing tertiary stereocenters are usually encoded into the structure with the help of a stoichiometric amount of a chiral auxiliary (Scheme 1 a, right).^[3] Popular solutions include the use of enolate alkylations reported by the groups of Evans^[4] and Myers.^[5] In addition, crotylation reported by the group of Brown^[6] and chiral pool methods are also occasionally used. Scheme 1 b summarizes some recent natural product targets and the methods used to construct the methyl-bearing tertiary stereocenters in them.^[7,8]

As an alternative to these stoichiometric methods, amine-catalyzed addition reactions of simple alkyl aldehydes to

a) Control of face selectivity in accessing tertiary stereocenters bearing methyl groups



b) Typical methods for installing Me stereocenters



Scheme 1. a) Access to methyl-substituted stereocenters through stereocontrol on the nucleophile (with a chiral auxiliary) or on the electrophile (with a chiral catalyst). b) Examples of chiral pool or chiral auxiliary methods for the construction of methyl-bearing stereocenters in natural products.

methyl vinyl ketone or to activated acrylates have been reported by the groups of Gellman^[9] and Maruoka.^[10] α -Alkylation of aldehydes^[11] can also provide access to aldehydes bearing α -substituents, but the simplest methyl substituents are still challenging and require indirect methods.^[12] While these solutions are attractive, and have already found use in total synthesis,^[13] they are all restricted to easily epimerizable α -chiral aldehydes.^[14]

To enable the catalytic, enantioselective synthesis of configurationally more stable α -alkyl carboxylic acid derivatives, we report here the successful design of a catalyst which allows the stereochemistry of a Mukaiyama–Michael reaction^[15] between acrolein and enolsilane (Scheme 1 a, left). This approach requires remote control of enantioface selectivity. We have previously reported successful enantioselective Mukaiyama–Michael reactions of acrolein with silyloxyfuran nucleophiles.^[16] Still, it remained far from certain whether the methodology could extend to enolsilanes (d^2

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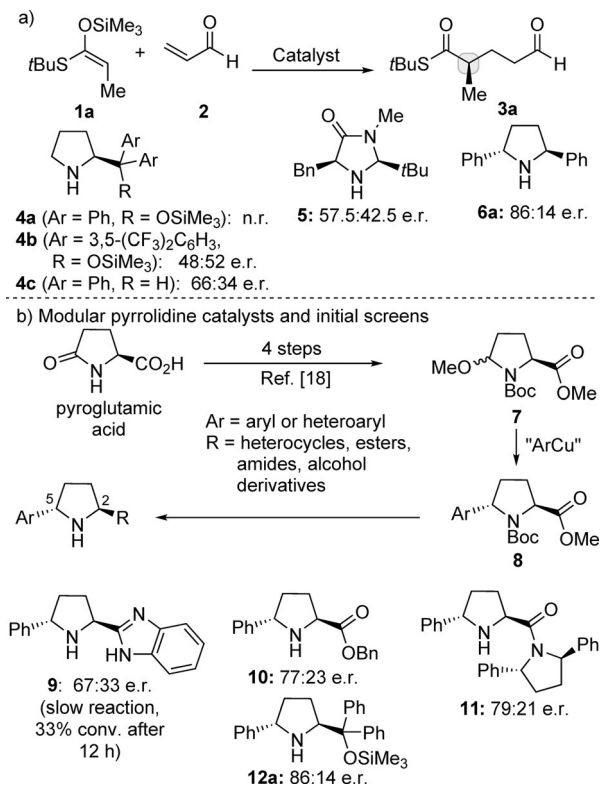
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nucleophiles), which present a much smaller contact area with the iminium electrophile compared to the silyloxyfurans (*d*⁴ nucleophiles).

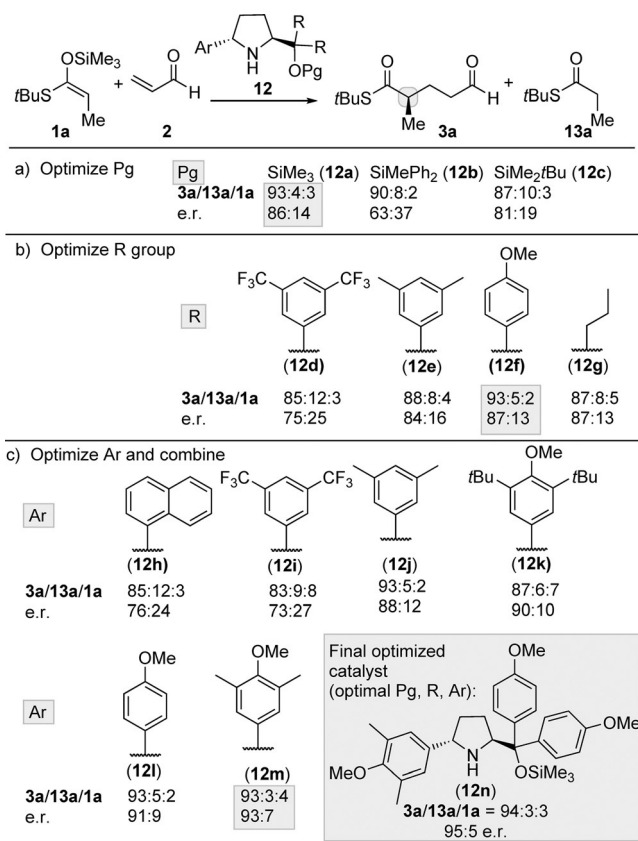
Indeed, in initial screens, the enolsilane **1a** and acrolein (**2**), in combination with our previously successful diarylpyrrolidine catalyst **6a**,^[16] afforded only moderate enantioselectivities (Scheme 2 a).^[17] Other iminium catalysts (e.g. **4a–c**



Scheme 2. a) Preliminary screens for suitable catalysts. Reaction conditions: Acrolein (**2**; 5 equiv), the catalyst **4–6** (0.2 equiv), 4-nitrobenzoic acid (0.2 equiv), H₂O (2 equiv), CH₂Cl₂, 0°C. The e.r. value was measured using GC analysis with a chiral stationary phase. b) Design of new *trans*-2,5-disubstituted pyrrolidine catalysts from pyroglutamic acid and evaluation of the first-generation designed catalysts in the Mukaiyama–Michael reaction. For details, and further examples, see the Supporting information. n.r. = no reaction.

or **5**) or aryl-substituted variants of **6** also turned out to be ineffective.^[17] However, pyroglutamic-acid-derived^[18] 2,5-disubstituted pyrrolidines, especially **12a** (Scheme 2b), appeared to be viable candidates for further optimization. Other designs (**9–11**) offered inferior selectivities.

Importantly, the design of **12** provided us with three independently tunable variables (the protecting group Pg, the R group, and the 5-aryl (Ar) group; Scheme 3). Increasing the size of the silyl protection (Pg) was not helpful (Scheme 3a). However, varying the R and Ar groups proved more fruitful and enhanced enantioselectivity. Most importantly, introduction of electron-donating groups (**12f** versus **12a** and **12m** versus **12a**) increased the e.r. value, while introduction of electron-withdrawing substituents on the phenyl ring (**12i**) led to decreased e.r. values. When this trend started to emerge from the data, we quickly arrived at the final catalyst **12n**,



Scheme 3. Design and optimization of the new catalyst family through a three-variable (Pg, R, Ar) tuning of the catalyst structure. Pg = protecting group.

which combined the separately optimized groups (Ar, R, and Pg) into a single catalyst structure. The catalyst **12n** afforded the product **3a** with 95:5 e.r. and excellent conversion.

Insight into the origin of enantioselectivity with **12n** was provided by DFT calculations for transition states of the C–C bond formation between the iminium intermediate **14** (derived from **12n** and **2**) and **1a** (Figure 1). The most favored transition states leading to the major (*R*) and minor (*S*) product are shown in Figure 1. The energy difference between these diastereomeric structures is related to the combined effect of repulsive steric and attractive noncovalent interactions, which varies for the two competing pathways.^[17] For catalysts **12i** and **12a**, the computations predicted higher, not lower selectivities compared to **12n** (the computed $\Delta\Delta G^\ddagger$ was 3.8 kcal mol^{−1} for **12i** vs 2.1 kcal mol^{−1} with **12n**). This apparent contradiction with the experimental trend might result if the more electron-poor catalyst **12i** could promote the reaction via an alternative, racemic mechanism^[19] (e.g. via acid catalysis). However, control experiments^[17] appear to rule out this possibility: neither carboxylic acids nor protonated amines with *pK_a* values close to that of **12i** (estimated *pK_a* 4.2) promoted the reaction. The divergence of the computed and experimental $\Delta\Delta G^\ddagger$ values could also indicate that the counterion (which was not included in the computations) may alter the energies of the pathways or even alter the mechanism.^[19]

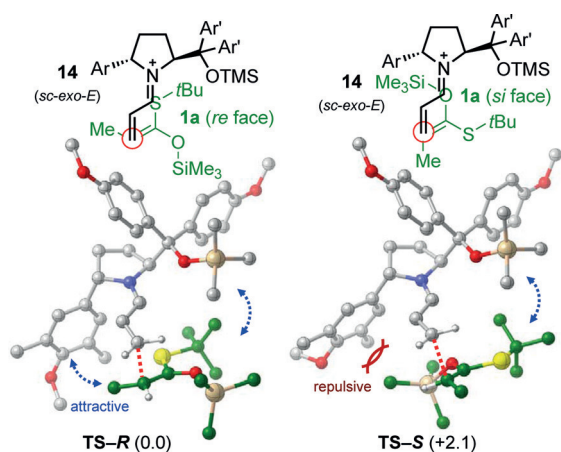


Figure 1. Diastereomeric transition states computed for reaction catalyzed by **12n**. Relative energies, in kcal mol⁻¹, are shown within parentheses. The developing C–C bonds are indicated by red dotted lines. Hydrogen atoms are omitted for clarity, except those of reacting carbon atoms. TMS = trimethylsilyl.

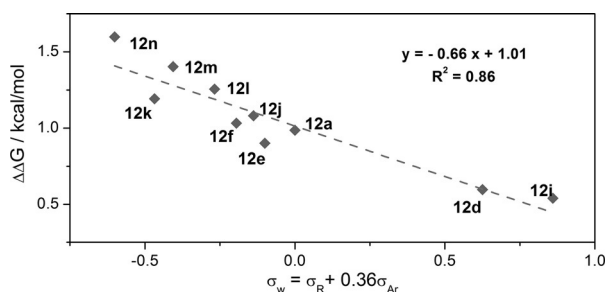


Figure 2. Correlations between the aryl substituents on the catalyst and the enantioselectivity. LFER correlating the weighted Hammett constants (σ_w) of aryl substituents with enantioselectivity. Herein, σ_R and σ_{Ar} refer to substituent constants associated with R and Ar groups, respectively. The coefficient 0.36 was obtained from a fitting procedure (see the Supporting Information).

The observed trend that led us to the structure of **12n** can also be expressed more quantitatively in the form of a linear free-energy relationship (LFER)^[20] relating the observed enantioselectivities (expressed as the free energy difference $\Delta\Delta G^\ddagger$) with the weighted Hammett constants (σ_w ; Figure 2). Interestingly, the LUMO energy of the iminium ion correlated reasonably with the enantioselectivity as well. Although these correlations do not explain the effect of the electron-donating substituents, they do confirm that the effect is nearly linear, and also serve as pointers for the design of future catalysts for similar transformations.^[21]

The scope of the Mukaiyama–Michael addition reaction on acrolein was investigated with various alkylated silyl ketene thioacetals (Table 1). The adduct **3a**, with a methyl group, was isolated in 70 % yield and 95:5 of e.r. Pleasingly, **3a** can also be obtained with the same enantioselectivity (95:5 e.r., 76 % yield) at lower catalyst loading (5 mol %). If the aldehyde is needed in protected form, in situ protection of **3a** gives the corresponding acetal **17a** in 76 % overall yield from **1a** (1 mmol scale, 94:6 e.r., see Scheme 4a). For other R

Table 1: Substrate scope for Mukaiyama–Michael reaction of alkylated silyl ketene thioacetals with acrolein.^[a]

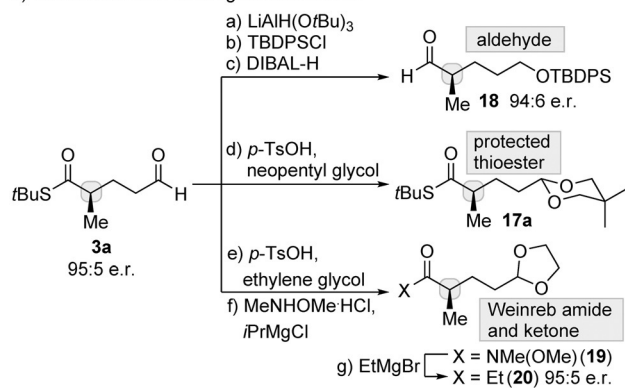
Entry	Product	R	1a Z/E	Yield [%] ^[b]	e.r. ^[c]
1	3a	Me	100:0	76 ^[d]	95:5
2	15b	Et	100:0	62	96.5:3.5
3	15c	<i>n</i> Bu	96:4	67	94.5:5.5
4	15d	<i>i</i> Bu	96:4	68	94.5:5.5
5	15e	<i>n</i> -C ₁₀ H ₂₁	100:0	69	94.5:5.5
6	15f	PhCH ₂ CH ₂	95:5	72	95.5:4.5
7	15g	BnOCH ₂ CH ₂	90:10	52	94:6
8	15h	BnO(CH ₂) ₃	97:3	67	94.5:5.5
9	16i	Allyl	95:5	60	94:6
10	15j	<i>i</i> Pr	91:9	61	97.5:2.5
11	15k	<i>c</i> -C ₆ H ₁₁	93:7	64	98:2
12	15l	<i>c</i> -C ₅ H ₉	93:7	60	97:3

[a] Reaction conditions: a) Acrolein (**2**; 5 equiv), catalyst **12n** (0.2 equiv), 4-nitrobenzoic acid (0.2 equiv), H₂O (2 equiv), CH₂Cl₂, 0 °C, 12 h; b) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*BuOH/H₂O, RT; c) LiAlH₄-(*O**t*Bu)₃, THF, 0 °C. [b] Yield of product after either oxidation or reduction. [c] Determined by HPLC analysis using a chiral stationary phase. For **3a**, the e.r. value was determined by GC analysis using a chiral stationary phase. [d] After 22 h with 0.05 equiv of **12n** and 0.05 equiv of 4-nitrobenzoic acid.

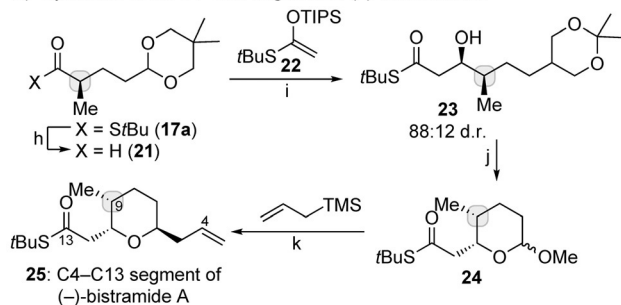
groups, the yields and enantiomeric ratios of the products were determined after oxidation of the aldehyde product in the corresponding carboxylic acid **15**, or after reduction to the alcohol **16** (Table 1). Access to functionalized thioesters with either long alkyl chains or remote readily tunable substituents (allyl, benzyloxy, aryl) is possible with good yields and excellent enantioselectivities ranging from 94:6 e.r. to 98:2 e.r. Importantly, the enantioselectivity of the reaction is not compromised by the presence of the *E* isomer impurity in **1**. Only the yield of the isolated product is affected, as the *E* isomer appears to be unreactive under the reaction conditions.

The versatility of the thioester group was first demonstrated by the straightforward conversion of the product **3a** into the key building block aldehyde **18** (Scheme 4a) with complete retention of enantiomeric purity. The aldehyde **18** has been frequently used in the total synthesis of natural products. Typically, its synthesis requires a stoichiometric amount of either a chiral pseudoephedrine^[22] or oxazolidinone^[23] auxiliary, or resorting to chiral pool sources, such as ozonolysis of a β -citronellene derivative.^[24] Chiral ketone building blocks can also readily be accessed from **3a** via the corresponding Weinreb amide **19**, which was smoothly converted into ethyl ketone **20** in 95:5 e.r. (Scheme 4a).

Finally, the synthetic utility of our methodology was illustrated by the straightforward access to the C4–C13 segment of bistramide A (Scheme 4b). To date, seven different routes for the total syntheses of the bistramides have been published.^[7a,25] Out of them, five synthetic routes, including

A) Access to chiral building blocks from **3a**

B) Synthesis of the C4–C13 fragment of (–)-Bistramide A



Scheme 4. A) Access to chiral building blocks from **3a**. Reagents and conditions: a) $\text{LiAlH}(\text{O}t\text{Bu})_3$, THF, -20°C , 3 h, 90% (63% based on **1a**); b) TBDPSCI, imidazole, DMF, RT, overnight, 95%; c) DIBAL-H, CH_2Cl_2 , -78°C , 45 min, 98%; d) $p\text{-TsOH}$ (0.1 equiv), neopentyl glycol (5 equiv), CH_2Cl_2 , 0°C , 15 h, 76% over two steps from **1a**; e) $p\text{-TsOH}$ (0.2 equiv), ethylene glycol (3 equiv), reflux overnight, 70% over two steps from **1a**; f) $\text{MeNHOMe}\cdot\text{HCl}$ (4.1 equiv), $i\text{PrMgCl}$ (8 equiv), 0°C , THF, overnight, 87%; g) EtMgBr (3 equiv), THF, 16 h, 0°C , quant. B) Synthesis of C4–C13 fragment of (–)-bistramide A. Reagents and conditions: h) DIBAL-H (1.8 equiv), CH_2Cl_2 , -78°C , 1 h, 93%; i) **22** (1.2 equiv), $\text{BF}_3\cdot\text{OEt}_2$ (2 equiv), -78°C , 4 h, 65%; j) $p\text{-TsOH}$ (0.2 equiv), MeOH , 50°C , 6 h, 84%; k) allyltrimethylsilane (5 equiv), BiBr_3 (0.5 equiv), RT, 12 h, 90%. DIBAL-H = diisobutylaluminum hydride, DMF = N,N -dimethylformamide, TBDPS = *tert*-butyldiphenylsilyl, Ts = 4-toluenesulfonyl.

the two most recent syntheses,^[7a,25b,c,e,f] use either chiral auxiliary or chiral reagents to access the C9 methyl-bearing stereocenter. We used the acetal **17a** as the starting material for a four-step synthesis of the C4–C13 fragment of the bistrames (**25**; Scheme 4b), with a diastereoselective Mukaiyama aldol^[26] and a BiBr_3 -promoted C-allylation^[27] of the tetrahydropyran **24** as the key steps. The fragment **25** was obtained in 31% overall yield starting from **17a**.

In summary, systematic probing of three independent variables afforded a successful catalyst which allows access to chiral thioesters, amides, aldehydes, and ketones bearing either α -methyl or other α -alkyl groups in high enantiomeric purity. The products are directly useful in natural product synthesis, as demonstrated by a rapid access to the C4–C13 segment of (–)-bistramide A. We anticipate that the three-point optimization procedure which led to the successful catalyst structure should inspire researchers to tackle other standing challenges in catalytic enantioselective synthesis.

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