Asymmetric organocatalytic Michael addition of azlactones to *cis*-1,2-bis(phenylsulfonyl)ethene. A simple entry to quaternary α-amino acids†‡

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Azlactones react with 1,2-bis(phenylsulfonyl)ethene under catalysis by simple chiral thioureas, affording α,α-disubstituted α-amino acid derivatives in good yields and in moderate to good enantioselectivities.

The synthesis of α,α-disubstituted quaternary α-amino acids has become a much pursued target in the past few years.[1] This important class of non-proteinogenic amino acids, upon incorporation into a peptide chain, can lead to peptides or proteins with improved pharmacological properties.[2] Moreover, they are present in antibiotics such as altemicidin[3] and they have also been found in carbonaceous meteorites.[4] Even if today we have several methods for the asymmetric preparation of quaternary α-amino acids,[1,5] most of them still present important limitations, both in terms of scope and of enantioselectivity.

Although the utility of racemic 4-substituted oxazol-5-(4*H*)-ones (azlactones) as precursors of highly enantioenriched α,α-disubstituted α-amino acids[6] was recognized almost simultaneously by Fu[7] and by Trost[8] more than a decade ago, it has been only after the "gold rush" of asymmetric organocatalysis[9] that azlactones have begun to show their full potential as masked amino acid nucleophiles. The first organocatalytic enantioselective alkylation of 4-substituted azlactones was reported in 2008 by Jørgensen and co-workers.[10] These authors found that, using chiral iminium catalysis,[11] racemic 4-substituted azlactones underwent Michael addition to α,β-unsaturated aldehydes with high diastereo- and enantioselectivities, and that the resulting C4-adducts were easily converted into optically active α,α-disubstituted α-amino acids and derivatives. Subsequently, the amine-catalyzed addition of azlactones to nitroalkenes was independently reported by Jørgensen *et al.*[12] and by our research group,[13] while Terada and co-workers described the enantioselective direct aldol-type reactions of azlactones with protonated enol ethers under chiral Brønsted acid catalysis.[14] Recently, Jørgensen's group has demonstrated that α,β-unsaturated acyl phosphonates can serve as masked ester or amide equivalents in their thiourea-catalyzed Michael additions with azlactones.,[15,16] However, recurrent drawbacks of these methodologies are the competing C2 azlactone alkylation,[12,13,15] and the presence of several functional groups in the final adducts, making the synthesis of α,α-dialkyl amino acids difficult. We have found a solution to these problems by using 1,1-bis(phenylsulfonyl)ethene as a Michael acceptor.[17] In effect, with the adequate choice of both the C2 azlactone substituent and of the reaction temperature, racemic 4-substituted azlactones react with 1,1-bis(phenylsulfonyl)ethene, in the presence of chiral bifunctional aminothiourea catalysts, with total C4 regioselectivity, and with good to excellent yields and enantioselectivities.[18] The resulting adducts can then be derivatized by addition of different electrophiles to the methyne disulfone moiety and/or by reductive removal of the sulfone groups,[19] to afford the "naked" alkyl chain (Scheme 1).

Very recently, Quintard and Alexakis reported on the use of 1,2-bis(sulfone)vinylenes in enamine catalysis.[20] Unexpectedly, these sulfones led to a rearrangement of the initially formed adduct **A** to the *gem*-disulfone **B** (Scheme 2).

Our attention was immediately caught by these results, and in the context of our interest in the organocatalyzed reactions of sulfones,[18,21,22] we envisioned that, due to its low cost and easy synthesis, *cis*-1,2-bis(phenylsulfonyl)ethene **1** could be used as a practical surrogate of its 1,1-regioisomer in the alkylation of racemic C4-substituted azlactones.

At the outset of our study we focused our attention on the addition of 2-(2,4-difluorophenyl)-4-isobutylazlactone **2h** to the 1,2-bis(sulfone)vinylene **1**, using triethylamine as base (Scheme 3). We were pleased to find that the expected rearranged C4-adduct **3h** was the major product. The C2-adduct **4h** and the C4-adduct **5h** were produced in minor amounts. These two compounds probably arise by phenylsulfone elimination from the rearranged intermediate, as previously suggested by Quintard and Alexakis.[20]

Next, we turned our attention to the asymmetric version of this reaction, and to this end we tested Takemoto and coworkers' thiourea-based catalyst (*S*,*S*)-**I**[23] in several solvents in the addition of azlactone **2a** to 1,2-bis(phenylsulfonyl)-ethene **1** (Table 1). In an initial screening, we found that toluene (entry 1) was the best solvent for the addition, since in other solvents such as dichloromethane (entry 2) or diethyl ether (entry 3) the conversion was good but the enantioselectivity was lower. It should be noticed that the use of more polar solvents such as ethyl acetate (entry 4) or acetonitrile (5) strongly decreased the rate of the reaction, probably because of the disappearance of the hydrogen-bonding catalysis of the thiourea moiety.[24] Most remarkably, the use of this

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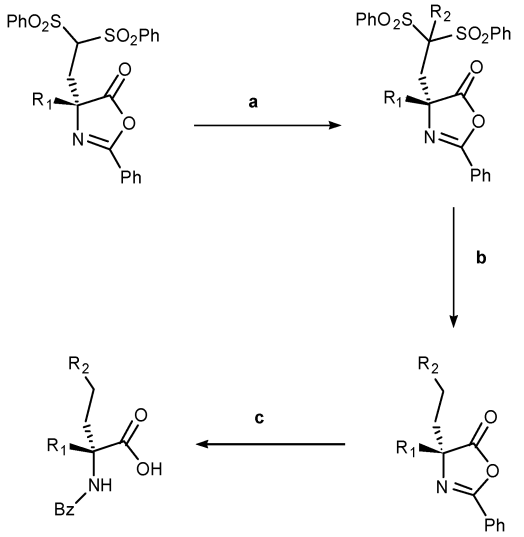
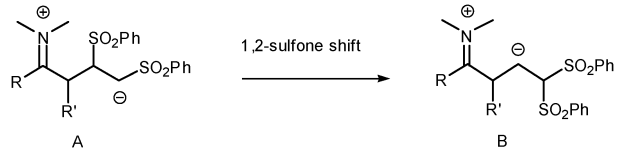


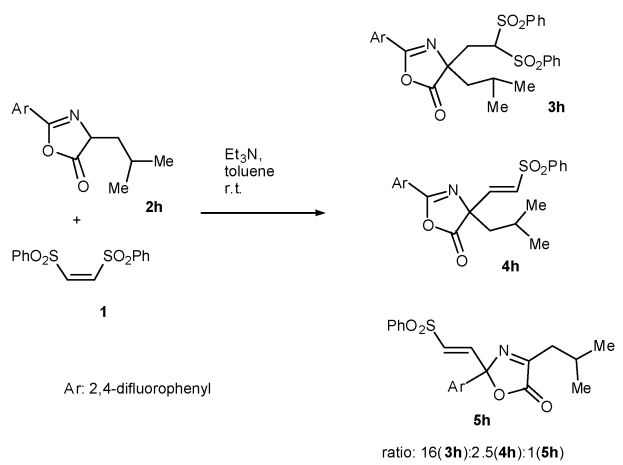
Scheme 1 Derivatization of the 1,1-bis(phenylsulfonyl)ethene-azlactone adducts. (a) NaH, THF; R^2I; (b) Mg, MeOH; (c) aq. HCl, acetonitrile.



Scheme 2 Sulfone rearrangement observed by Quintard and Alexakis (ref. 20).

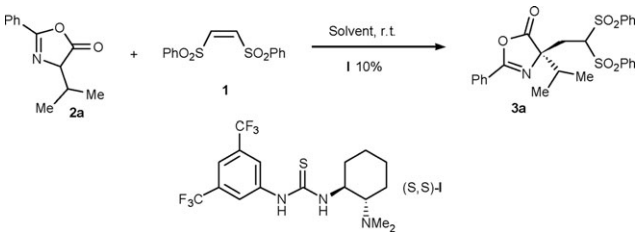
bifunctional amino-thiourea catalyst increased the selectivity of the process, and neither C2-adducts nor elimination products were detected in the reaction crude.

Later, we decided to study different catalysts (Table 2). When bifunctional thiourea catalysts such as **II** or **III** were used, the reaction rendered the final compounds with good conversions and good to moderate enantioselectivities (entries 6 and 7). On the opposite hand, when chiral bases such as quinine, quinidine, $(DHQD)_2AQN$ (**IV**) or $(DHQD)_2PHAL$ (**V**) were used, no reaction was observed (entries 1–4). In order to improve the enantioselectivity of the reaction, we ran the



Scheme 3 Reaction of **1** and **2h** with Et_3N in toluene.

Table 1 Solvent screening



Entry	Solvent	Conversion 24 h (%)[a]	ee (%)[b]
1	Toluene	60	88
2	CH_2Cl_2	72	59
3	Et_2O	70	rac
4	AcOEt	Traces	67
5	ACN	Traces	55

[a] Determined by ^{1}H-NMR of the crude mixture. [b] Determined by chiral HPLC.

addition at low temperature, but unfortunately when the reaction was performed at −20 °C or even at 4 °C no product was observed after 14 h (entries 8–9). These data show again the importance of the hydrogen-bonding by the thiourea moiety, that clearly activates the 1,2-bis(phenylsulfonyl)ethylene towards the attack of the azlactone anion.

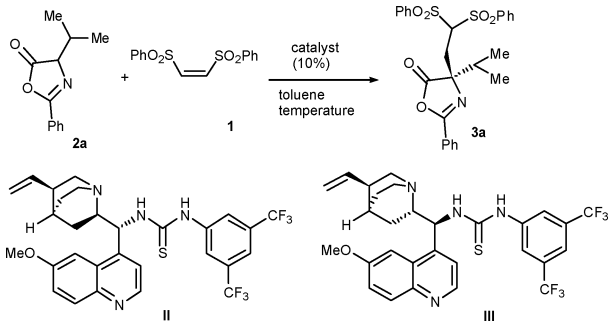
With these conditions on our hands, we decided to study the effect of the nature of the C2-azlactone substituent (Table 3). As previously noted by Jørgensen *et al.*[12] and by us,[18] the presence of fluorine atoms in the aromatic ring becomes crucial in order to achieve high enantioselectivities; thus, when 2,4-difluorophenyl was used, the enantioselectivity increased up to a 95% ee (entry 5). However, when other fluoro substitution pattern was used or with a chloro substituent the enantioselectivity decreased (entries 2–4). Remarkably, when a *tert*-butyl was used as the C2 substituent, the reaction became sluggish and no final product was isolated (entry 6).

Finally, we explored the scope of the reaction by using different substituents at the C4 azlactone position (Table 4).

In order to ascertain the absolute configuration of the addition products, compound **3a** was correlated to our previous work with 1,1-bis(phenylsulfonyl)ethene.[18] The enantioselective sense of the reaction was the same: when (*S*,*S*)-**I** was used as the catalyst, azlactone **2a** reacted with *cis*-1,2-bis(phenylsulfonyl)ethene **1**, affording the (*S*)-4-(2,2-bis(phenylsulfonyl)ethyl)-4-isopropyl-2-phenyloxazol-5(4*H*)-one **3a**. This result can be rationalized by the transition state depicted in Fig. 1, where the tertiary amine deprotonates the azlactone while the thiourea moiety is activating the vinyl sulfone by hydrogen-bonding.

In conclusion, we have reported a new, practical and enantioselective entry to direct precursors of quaternary α-alkyl-α-amino acids based in organocatalysis. The reaction of racemic C4-substituted azlactones **2** with *cis*-1,2-bis(phenylsulfonyl)-ethene **1** is efficiently catalyzed by chiral bifunctional amino-thioureas. The overall process (Michael addition followed by 1,2-sulfone rearrangement) takes place with complete C4 regioselectivity and with good yields and moderate to good enantioselectivities. Moreover, this methodology is complementary to

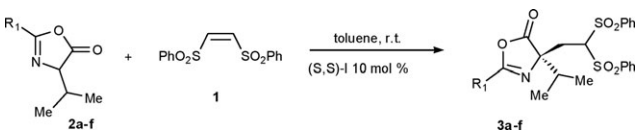
Table 2 Conditions and temperature screening



Entry	Catalyst	Temp. (°C)	Conversion (24 h) (%)[a]	ee (%)[b]
1	$(DHQD)_2AQN$(IV)	r.t.	0	—
2	$(DHQD)_2PHAL$(V)	r.t.	0	—
3	Quinine(VI)	r.t.	0	—
4	Quinidine	r.t.	0	—
5	(S,S)-I	r.t.	60	88
6	II	r.t.	74	−32
7	III	r.t.	12	75
8	(S,S)-I	4	Traces	—
9	(S,S)-I	−20	0	—

[a] Determined by ^{1}H-NMR of the crude reaction mixture. [b] Determined by chiral HPLC.

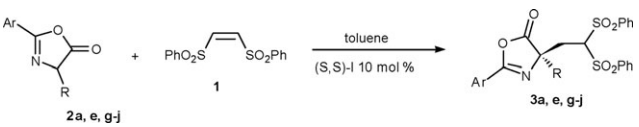
Table 3 C-2 substituent screening



Entry	R_1	Product	t/h	Yield (%)[a]	ee (%)[b]
1		**3a**	48	76	88
2		**3b**	24	50	54
3		**3c**	48	81	74
4		**3d**	48	63	75
5		**3e**	48	73	95
6	t-Bu	**3f**	48	Traces	—

[a] Isolated product. [b] Determined by chiral HPLC.

Table 4 Scope of the reaction



Entry	Ar	R	Product	t/h	Yield (%)[a]	ee (%)[b]
1		i-Pr	**3a**	48	76	88
2		i-Pr	**3e**	48	73	95
3		Me	**3g**	72	73	75
4		i-Bu	**3h**	72	97	74
5		t-Bu	**3i**	48	82	68
6	t-Bu	Ph	**3j**	96	45	75

[a] Isolated product. [b] Determined by chiral HPLC.

previously reported enantioselective approaches to quaternary α-amino acids, allowing the synthesis of α-phenyl-α-alkyl-α-amino acids and of α-*tert*-butyl-α-alkyl-α-amino acids. Therefore, the procedure presented here has distinct advantages in terms of operational simplicity, environmentally friendly conditions and suitability for large-scale reactions for practical industrial preparations. Studies on the mechanism and the

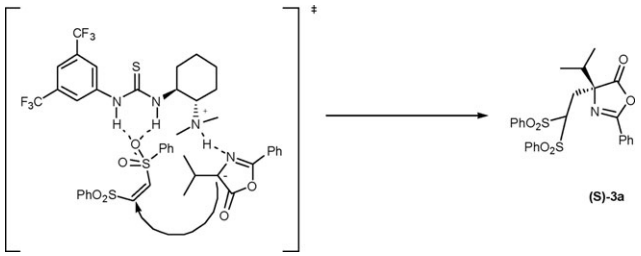


Fig. 1 Proposed transition state.

application of this new methodology in total synthesis are currently ongoing in our laboratory.

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Notes and references

‡ Experimental Section

To a flask containing a solution of the oxazol-5-one (0.078 mmol, 1.5 equiv.) and the corresponding catalyst (0.0052 mmol, 0.1 equiv.) at the desired temperature in toluene (0.5 mL), 1,2-bis(phenylsulfonyl)-ethylene (16 mg, 0.052 mmol, 1 equiv.) was added in one portion. The reaction mixture was stirred at this temperature after completion. The crude was purified by column chromatography to afford compound **3**.

3a: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 2H), 8.01–7.98 (m, 2H), 7.83–7.81 (m, 2H), 7.64–7.51 (m, 6H), 7.44–7.39 (m, 2H), 5.05 (dd, J = 8.2 Hz, J = 2.6 Hz, 1H), 2.89 (dd, J = 16.4 Hz, J = 2.3 Hz, 1H), 2.74 (dd, J = 16.1 Hz, J = 7.9 Hz, 1H), 2.08 (h, J = 6.7 Hz, 1H), 0.98 (d J = 6.7 Hz, 1H), 0.95 (d, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9, 162.0, 137.3, 136.9, 134.7, 134.6, 133.1, 130.0, 129.7, 129.1, 128.8, 128.2, 79.3, 72.3, 37.4, 30.9, 29.5, 16.4,; HRMS (ESI): calcd. for $[M+H]^+$ ($C_{26}H_{26}NO_6S_2$) requires 512.1196, found 512.1198. HPLC (Chiralpak IA, n-hexane : i-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 9.5, 12.4 min. $[\alpha]_D^{25}$ = −11.2 (c = 0.77, $CHCl_3$, 95% ee).

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