Asymmetric Catalysis

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Catalytic Asymmetric Synthesis of α-Quaternary Proline Derivatives by 1,3-Dipolar Cycloaddition of α-Silylimines**

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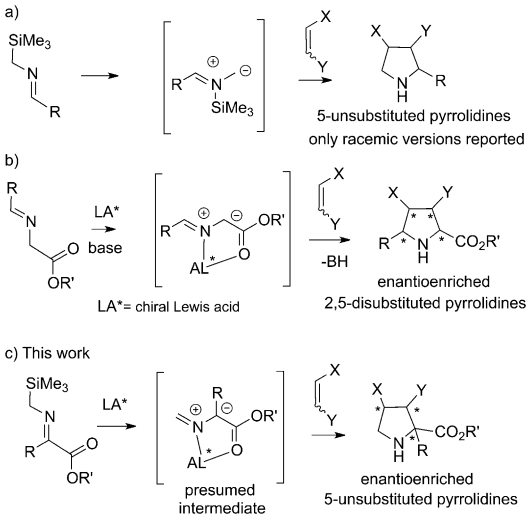
In memory of Christian G. Claessens

Pyrrolidines and derivatives are privileged scaffolds in synthetic and medicinal chemistry, and are present in a myriad of natural products and biologically active compounds.[1] In particular, modified proline derivatives have been extensively used as conformationally rigid cores in peptidomimetics.[2] In this area, α-quaternary amino acids have received great attention since this type of unit improves the lipophilicity and restricts the conformational flexibility of the peptidic chain, and therefore has a great impact in the biological activity.[3] Furthermore, α-quaternary prolines have found wide application as chiral synthons and organocatalysts in organic synthesis.[4] As a consequence, a variety of strategies for their enantioselective preparation, mainly based on the funtionalization of L-proline, have been reported.[5] Despite this progress, the development of efficient asymmetric methodologies to access densely substituted α-quaternary prolines are still in high demand.

The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with activated olefins is one of the most reliable and straightforward approaches to the preparation of optically active highly substituted 2-carboxylate pyrrolidine derivatives. Since the seminal contributions of Zhang and co-workers[6] and Jørgensen and co-workers[7] in the metal-catalyzed enantioselective preparation of 2,5-disubstituted pyrrolidine derivatives using Schiff bases of amino acid esters as azomethine precursors, outstanding progress has been achieved in this research area.[8,9] In this context, and because of its high reactivity, glycinate imines are the most frequently employed azomethine ylide precursors in this reaction.[10,11]

α-Silylimines constitute a different and much less studied type of azomethine ylide precursor, which leads to 5-unsubstituted pyrrolidines,[12] a substitution pattern not accessible by the typical process from Schiff bases of amino acid esters (Scheme 1 a). However, despite this structural interest, as far as we are aware, their use in catalytic asymmetric processes remains undocumented.



Scheme 1. 1,3-Dipolar cycloaddition of α-silylimines.

The great efficiency of Schiff bases of amino acid esters as azomethine ylide precursors relies on the formation of a rigid five-membered N,O-bidentate metalated azomethine (Scheme 1 b). Thus, we reasoned that the presence of a coordinating group in the α-silylimine, such as an ester moiety, could enhance the reactivity and stereoselectivity of the process by means of the formation of a presumed five-membered metalated intermediate, which would approach the chiral ligand to the reactive center (Scheme 1 c). With the aim of expanding the scope of the pyrrolidine adducts accessible by catalytic asymmetric 1,3-dipolar cycloaddition, we report herein the first enantioselective procedure involving α-silylimines as azomethine precursors to provide 5-unsubstituted quaternary proline derivatives.

To evaluate the viability of the process, we chose as a model reaction the cycloaddition of ethyl-(trimethylsilyl)-methyliminopropanoate (**1a**) with *N*-phenylmaleimide (**2**; Table 1). We began our investigation by examining the silver-catalyzed reaction in the presence of a variety of chiral ligands in toluene as the solvent. Although good yields and high diastereoselectivities were obtained with the chiral ligands **4**–

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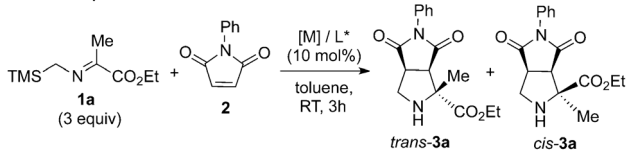
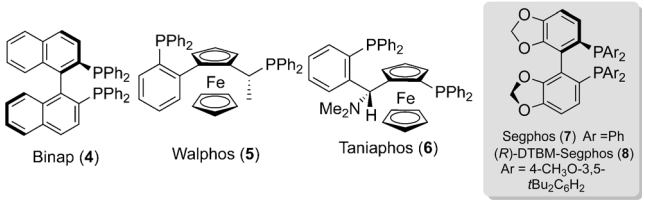
Table 1: Optimization studies for the model reaction.





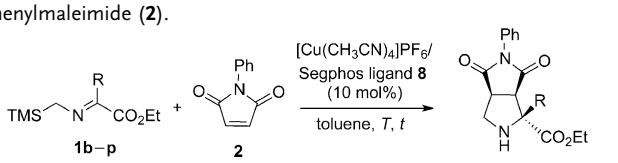
Entry	Metal source [M]	L*	Yield [%][a]	*trans*/*cis*[b]	*ee* [%][c]
1	AgOAc	**4**	57	10:90	0
2	AgOAc	**5**	68	10:90	0
3	AgOAc	**6**	75	10:90	0
4	AgOAc	**7**	72	10:90	0
5	AgOAc	**8**	73	>95:5	81
6	$Cu(OAc)_2$	**8**	–	–	–
7	CuOAc	**8**	66	>95:5	88
8	CuBr	**8**	56	>95:5	92
9	$CuPF_6$[d]	**8**	71	>95:5	92
10[e]	$CuPF_6$[d]	**8**	40	>95:5	92
11[f]	$CuPF_6$[d]	**8**	45	>95:5	82

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC. [d] $CuPF_6 = [Cu(CH_3CN)_4]PF_6$. [e] Reaction carried out with 1.5 equiv of **1a.** [f] 5 mol% of catalysts. TMS = trimethylsilyl.

7, disappointingly, the pyrrolidine adduct **3a** was obtained in racemic form (entries 1–4). Interestingly, a complete inversion in the *cis*/*trans* diastereoselectivity and a remarkable 81% *ee* was observed in the presence of the bulkier and more electron-rich DTBM-Segphos ligand **8** (entry 5). Further optimization of the reaction conditions with this ligand was then undertaken. We observed a substantial enhancement in the enantioselectivity upon employing Cu^I salts as catalysts (entries 7–9), and in particular $[Cu(CH_3CN)_4]PF_6$ provided the best result (entry 9). The use of other solvents[13] or the presence of an external base was less effective. We also confirmed that the presence of 3 equivalents of the silylimine was necessary to obtain good yields (a moderate 40% yield was obtained using 1.5 equivalents of the silylimine; entry 10). The cycloaddition can be also performed with a lower catalyst loading (5 mol%), albeit with significant erosion in the reactivity and the enantioselectivity (entry 11).[14]

With these optimized reaction conditions, we next studied this cycloaddition with a variety of substituted silylimines. As summarized in Table 2, the reaction worked well for alkyl-substituted α-silylimines, thus affording the *trans* isomers with nearly complete diastereoselectivity (only the *trans* isomer was detected by ^{1}H NMR spectroscopy) and excellent enantioselectivity (entries 1–3). Similarly, the catalytic system was effective with a variety of *para*-substituted aromatic silylimines having both electron-donating and electron-withdrawing substituents (entries 4–9), as well as *meta*-substituted aromatic substrates (entries 10 and 11). The stereochemical

Table 2: Scope of the 1,3-dipolar cycloaddition of α-silylimines with *N*-phenylmaleimide (**2**).

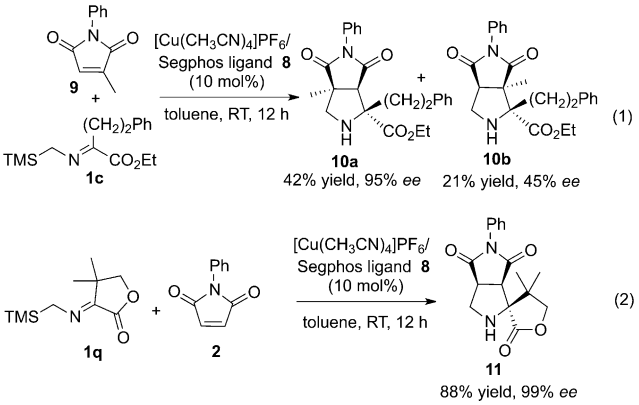


Entry	R	*T* [°C]	*t* [h]	Product	Yield [%][a,b]	*ee* [%][c]
1	*i*Bu	RT	3	**3b**	58	92
2	$Ph(CH_2)_2$	RT	3	**3c**	78	98
3	$CH_2=CH(CH_2)_2$	RT	12	**3d**	80	96
4	Ph	RT	3	**3e**	61	93
5	4-MeC_6H_4	60	12	**3f**	64	94
6	4-ClC_6H_4	60	12	**3g**	60	93
7	4-FC_6H_4	60	12	**3h**	45	92
8	4-CNC_6H_4	60	12	**3i**	65	92
9	4-$MeOC_6H_4$	RT	12	**3j**	79	96
10	3-MeC_6H_4	60	12	**3k**	64	95
11	2-napht	60	12	**3l**	78	94
12	2-ClC_6H_4	60	12	**3m**	–[d]	
13	mesityl	60	12	**3n**	–[d]	
14	H	RT	3	**3p**	50	81

[a] Yield of isolated product. [b] Only the *trans* isomer was detected by ^{1}H NMR spectroscopy. [c] Determined by HPLC. [d] No cycloaddition product was detected. RT = room temperature.

and configurational assignment of **3g** was unequivocally established by X-ray diffraction analysis.[15] In contrast, no cycloaddition product was isolated from the sterically more demanding *ortho*-substituted aromatic silylimines **1m** and **1n** (entries 12 and 13). Finally, the unsubstituted silylimine **1p**, derived from ethyl glyoxalate, was also a suitable substrate, albeit proceeding with a lower enantioselectivity (entry 14).

Interestingly, the cycloaddition also proceeded with the nonsymmetrical and more sterically demanding *N*-phenyl-3-methylmaleimide (**9**). The reaction with silylimine **1c** afforded a 2:1 mixture of regioisomers of the corresponding pyrrolidines bearing two quaternary stererocenters [Scheme 2, Eq. (1)]. The major regioisomer, **10a**, was isolated in 42% yield and excellent enantioselectivity (95% *ee*), whereas the isomer **10b** having two adjacent quaternary

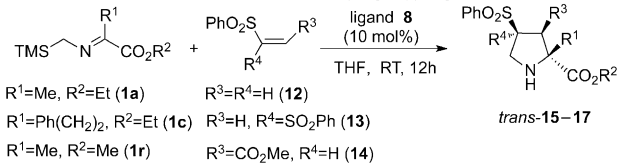


Scheme 2.

stereocenters was obtained in 21% yield and 45% *ee*. In view of the good reactivity profile of this catalyst system, we next turned our attention to the challenging cyclic silylimines. Pleasingly, the reaction with the α-silylimine **1q** proceeded smoothly, thus leading to the pyrrolidine spirolactone[16] **11** with excellent yield and complete diastereo- and enantioselectivity [Scheme 2, Eq. (2)].

Finally, to further explore the scope of this asymmetric [3+2] cycloaddition of α-silylimines we extended the study to acyclic dipolarophiles. Given the excellent properties of the sulfonyl group both as an electron-withdrawing group and as an easily removed substituent,[17] we tested a variety of α,β-unsaturated sulfones as olefin partners (Table 3). The reaction of the silylimines **1a** and **1c** with phenylvinylsulfone (**12**)

Table 3: 1,3-Dipolar cycloaddition of α-silylimines with vinylsulfones.

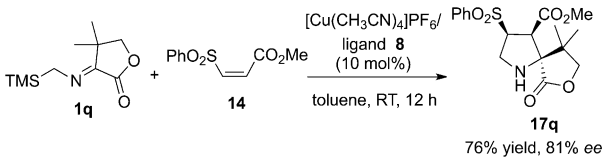


Entry	R^1	R^2	R^3	R^4	Product	Yield [%][a]	*ee* [%][b]
1[c]	Me	Et	H	H	**15a**	48	55
2	Me	Et	H	H	**15a**	75	83
3	$Ph(CH_2)_2$	Et	H	H	**15c**	72	94
4	Me	Et	H	SO_2Ph	**16a**	70	73
5[d]	Me	Et	H	SO_2Ph	**16a**	78	79
6	Me	Et	CO_2Me	H	**17a**	80	97
7	$Ph(CH_2)_2$	Et	CO_2Me	H	**17c**	78	97
8	Me	Me	CO_2Me	H	**17r**	89	99

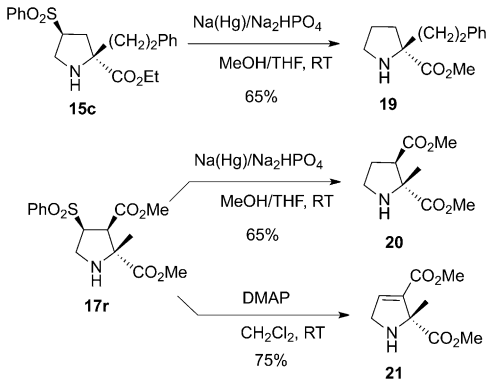
[a] Yield of isolated product. [b] Determined by HPLC. [c] Reaction performed in toluene. [d] (*R*)-MeO-biphep was used as the ligand; see the Supporting Information for the ligand structure.

under the optimized reaction conditions (but using THF as the solvent), afforded the corresponding sulfonyl pyrrolidines **15a** and **15c** with excellent diastereoselectivity (only the *trans* diastereomers were detected by ^{1}H NMR spectroscopy), and 83% and 94% *ee*, respectively (entries 2 and 3). The reaction of **1a** with 1,1-(bissulfonyl)ethylene (**13**) also proceeded efficiently, thus leading to the adduct **16a** in 73% *ee* (entry 4). In this case, the asymmetric induction was enhanced to 79% *ee* when the MeO-biphep ligand was used (entry 5). Encouraged by these results we also tested the unsymmetrically disubstituted *Z*-sulfonyl acrylate **14**.[18] The [3+2] cycloadditions with the silylimines **1a**, **1c**, and **1r**, catalyzed by Cu^I/DTBM-segphos, took place with nearly complete regioselectivity, diastereoselectivity, and enantioselectivity (entries 6–8). According to the previous results from our research group in other 1,3-dipolar cycloadditions of *Z*-sulfonyl acrylates, the regioselectivity was controlled by the sulfonyl group.[19] We also tested the cycloaddition of the cyclic α-silylimine **1q** with dipolarophile **14**, thereby providing the pyrrolidine spirolactone **17q** as a single isomer in 81% *ee* (Scheme 3).

The usefulness of sulfonylpyrrolidines to provide α-quaternary proline derivatives was next demonstrated by the desulfonylation reactions shown in Scheme 4. The pyrrolidines **19** and **20** were obtained by reductive cleavage of the sulfonyl group without any detectable epimerization by treatment with Na(Hg). It is interesting to note that the 2,3-dicarboxylate ester pyrrolidine **20** displays the opposite regioselectivity to that obtained using typical acrylate dipolarophiles.[20] In contrast, the basic elimination of the sulfonyl group of **17r** provided the pyrroline **21** selectively.

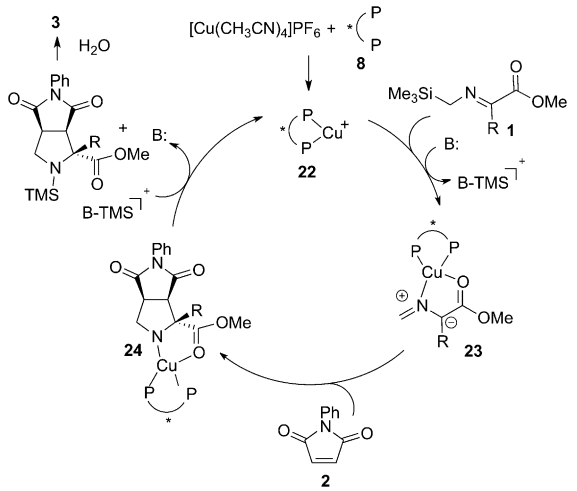


Scheme 3.



Scheme 4. Desulfonylation reactions. DMAP = 4-dimethylaminopyridine

To gain some insight into the reaction mechanism of this cycloaddition, some experiments were conducted. First, the reaction of the silylimine **1a** with *N*-phenylmaleimide (**2**) catalyzed by $[Cu(CH_3CN)_4]PF_6$/DTBM-Segphos was monitored by ESI-MS (Scheme 5; R = Me). After 10 minutes we were able to detect the presumed ions corresponding to the Cu/DTBM-Segphos complex **22** (*m*/*z* 1241.6), Cu/DTBM-Segphos/desilylated azomethine complex **23** (*m*/*z* 1370.7), and



Scheme 5. Proposed mechanism.

Cu/DTBM-Segphos/cycloaddition product **24** (*m*/*z* 1543.7; see the Supporting Information for details). These data suggest that the desilylation step, presumably promoted by the excess of imine substrate, takes place before the cycloaddition reaction. Accordingly, when silyl scavengers such as pyridine, 2,6-lutidine or CsF were used as additives the amount of the starting sylilimine **1** could be reduced from 3 to 1.5 equivalents to achieve full conversion.[21] On the basis of these data, a simplified plausible mechanism is shown in Scheme 5. Coordination of the silylimine **1** to the chiral DTBM-Segphos/Cu^{I} catalyst **22** and desilylation (promoted by the excess of starting imine **1** or an external base such as pyridine, 2,6-lutidine, or CsF) would lead to the key metal-bound azomethine ylide dipole **23**, whose subsequent cycloaddition with **2** would provide the pyrrolidine product and the recovery of the catalyst **22**.

In summary, an efficient catalytic asymmetric protocol for the Cu^{I}-catalyzed 1,3-dipolar cycloaddition of α-silylimines and activated olefins has been described. A variety of α-quaternary proline derivatives were obtained with good yields and excellent levels of diastereoselectivity and enantiocontrol with a variety of dipolarophiles, such as maleimides (up to 99% *ee*) and α,β-unsaturated sulfones (up to 99% *ee*). The use of the bulky DTBM-Segphos ligand proved to be crucial for attaining this high enantioselectivity.

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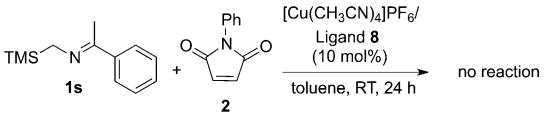
[14] No cycloaddition was observed under the optimal reaction conditions with the phenyl-substituted α-silylmine **1s**, thus showing the key activating role of the ester moiety.



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[20] This pyrrolidine substitution pattern is found in natural and biologically active compounds. For selected references, see: a) K. Shimamoto, Y. Shigeri, *Cent. Nerv. Syst. Agents Med. Chem.* **2006**, *6*, 59; b) H. Bräuner-Osborne, L. Bunch, N. Chopin, F. Couty, G. Evano, A. A. Jensen, M. Kusk, B. Nielsen, N. Rabaso, *Org. Biomol. Chem.* **2005**, *3*, 3926; c) J. M. Ndungu, J. P. Cain, P. Davis, S.-W. Ma, T. W. Vanderah, J. Lai, F. Porreca, V. J. Hruby, *Tetrahedron Lett.* **2006**, *47*, 2233.
[21] Compared with the standard reaction conditions involving 3 equivalents of silyl imine, in the presence of pyridine, 2,6-lutidine, or CsF desilylating agents we observed an erosion in the enantioselectivity of the process (91%, 90%, and 51% *ee*, respectively).

