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Enantioselective Synthesis of α-Heteroarylpyrrolidines by Copper-Catalyzed 1,3-Dipolar Cycloaddition of α-Silylimines

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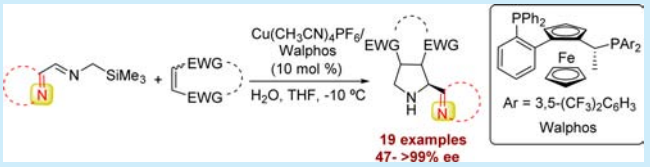
Supporting Information

ABSTRACT: α-Heteroarylpyrrolidines have been efficiently prepared via 1,3-dipolar cycloaddition between silylimines and activated olefins. In the presence of $Cu(CH_3CN)_4PF_6$/Walphos as catalytic system, high levels of enantioselectivity (up to ≥99% ee) and diastereoselectivity were achieved (major formation of C-2/C-4 *trans*-substituted pyrrolidines). The reaction is compatible with a broad variety of dipolarophiles including maleimides, maleates, fumarates, nitroalkenes, and vinylsulfones. The resulting cycloadducts can be transformed into bioactive pyrrolidine derivatives.



Pyrrolidines are considered to be important pharmacophores widely used in drug design.[1] In particular, the α-heteroarylpyrrolidine skeleton is present in a large number of natural products and biologically active compounds. Examples include nicotine[2] and analogues[3] (such as α-nicotine[4] and ABT 418[5]), (*R*)-harmicine,[6] BIRZ-227,[7] and 3-hydroxy-11-norcytisine[8] (Figure 1). All these α-heteroarylpyrrolidines have in common the absence of substitution at C-5 at the pyrrolidine unit.

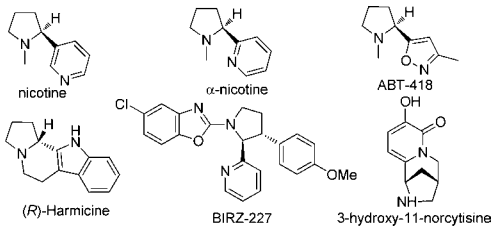
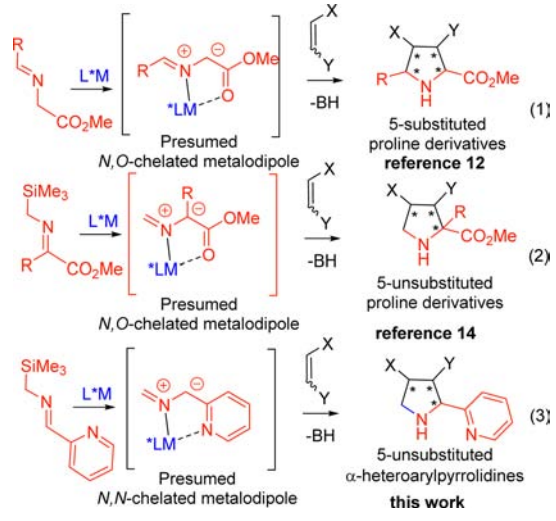


Figure 1. Selected examples of biologically active heteroarylpyrrolidines.

In addition, α-arylated pyrrolidines have found broad application as ligands and organocatalysts in asymmetric synthesis.[9] Despite the interest of these compounds, except for a few examples,[10] the approaches reported for its enantioselective preparation are usually based on the use of chiral auxiliaries.[11]

Among the current methods for the asymmetric synthesis of pyrrolidines, the enantioselective metal-catalyzed 1,3-dipolar cycloaddition of azomethine ylides has emerged as one of the most powerful.[12] However, although great progress has been recently achieved in this field, the structural scope of this enantioselective cycloaddition is usually restricted to the use of Schiff bases of amino acid esters[12] or related imines as dipole precursors[13] to provide 5-substituted pyrrolidine derivatives (Scheme 1, eq 1).

Scheme 1. Rational Design for the Synthesis of α-Heteroarylpyrrolidines



We have recently developed an enantioselective procedure to furnish 5-unsubstituted proline derivatives[14] by using *N*-(trimethylsilyl)methylimines of pyruvic esters (Scheme 1, eq 2). With these results in mind, we envisaged that a potentially coordinating heterocyclic moiety could act as an activating group in silylimine cycloadditions, generating a presumed *N*,*N*-chelated chiral metalodipole that would lead to the desired 5-unsubstituted α-heteroarylpyrrolidine (Scheme 1, eq 3). This type of asymmetric cycloaddition would represent a very direct way for the asymmetric synthesis of α-heteroarylpyrrolidines.

As model reaction we chose the cycloaddition of the silylimine **1a**, prepared from picolinealdehyde, with *N*-phenyl-

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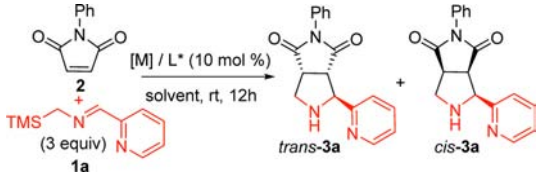
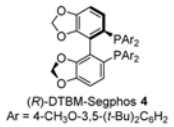
maleimide. Initially, we examined our previously reported conditions for 1,3-dipolar cycloaddition of pyruvate-derived α-silylimines[14] (3 equiv of silylimine, $Cu(CH_3CN)_4PF_6$ as metal source, DTBM-Segphos (**4**) as ligand and toluene as solvent, at room temperature). Even though the desired pyrrolidine **3a** was obtained in 70% yield, the cycloaddition occurred with extremely poor diastereoselectivity and enantioselectivity (Table 1, entry 1). The use of a silver catalyst (AgOAc)

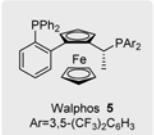
Table 1. Reaction Conditions for the Model Reaction



entry	[M]	solvent	L*	*trans*/*cis*[a]	yield[b] (%)	ee (*trans*)[c] (%)
1	$CuPF_6$[d]	toluene	**4**	50/50	70	<2
2	AgOAc	toluene	**4**	61/39	39	<2
3	$CuPF_6$[d]	toluene	**5**	52/48	72	75
4	$CuPF_6$[d]	CH_2Cl_2	**5**	50/50	63	79
5	$CuPF_6$[d]	THF	**5**	50/50	84	85
6[e]	$CuPF_6$[d]	THF	**5**	70/30	62	95

[a]Determined by ^{1}H NMR. [b]Isolated yield. [c]Determined by HPLC. [d]$CuPF_6$ = $Cu(CH_3CN)_4PF_6$. [e]Reaction at −10 °C.



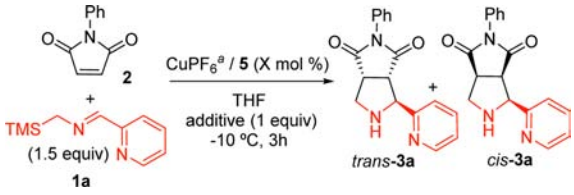


produced a significant decrease in the reactivity without improving the selectivity (entry 2). We next screened a structurally varied set of commercially available chiral ligands under Cu-catalyzed conditions in toluene as solvent,[15] finding out that Walphos ligand **5** provided the best enantioselectivity (entry 3, 75% ee). A further enhancement of the enantioselectivity and diastereoselectivity was observed using THF as solvent at −10 °C (*trans*/*cis* 70/30, 95% ee, entry 6).

We had previously observed with silylimines derived from pyruvic esters that the use of Lewis bases played a significant role in the process.[14] Thus, we next investigated the influence of silyl scavengers in the cycloaddition (Table 2). In the presence of several Lewis bases the amount of the starting silyl amine could be reduced from 3 to 1.5 equiv while maintaining good levels of reactivity (entries 1−4). Among the additives tested, water afforded the best enantioselectivity and similar results were obtained using either 1 or 5 equiv of water (entries 5 and 6, 96% ee and 97% ee). The cycloaddition can be also performed using a lower catalyst loading ($CuPF_6$/Walphos, 5 mol % instead of 10 mol %) albeit with a significant erosion of the enantioselectivity (entry 7).

To demonstrate the scope of the cycloaddition a variety of silylimines bearing diverse heterocyclic substituents were subjected to the optimized reaction conditions[16] (Scheme 2). In all cases, the cycloadditions took place with very high diastereoselectivity (*trans*/*cis* >95:<5), providing the *trans* adduct in good isolated yield (47−96% yield) and with high enantioselectivity regardless of the electronic nature and position of the substituents (82−98% ee). The absolute and relative configuration of pyrrolidine **3k**, obtained by reaction

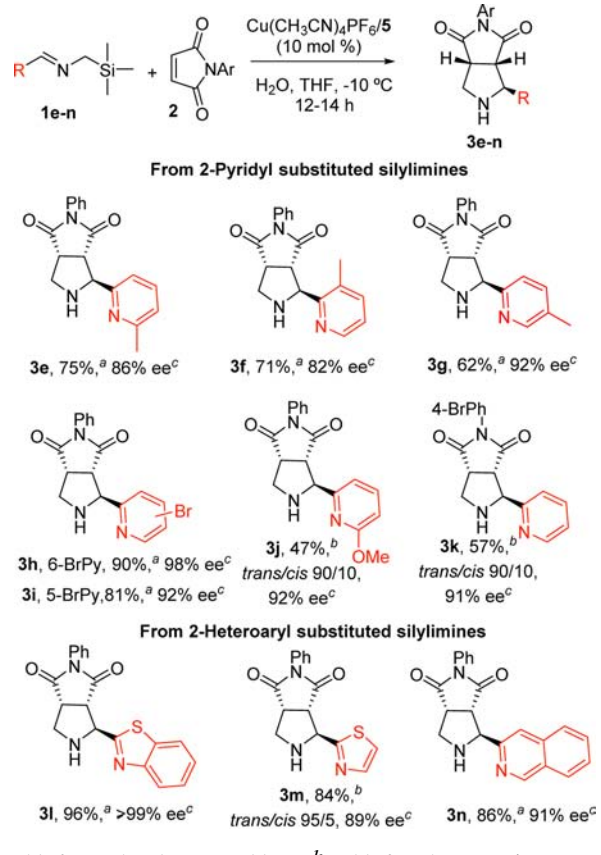
Table 2. Influence of Lewis Bases in the Cycloaddition



entry	additive	*X* (mol %)	*trans*/ *cis*[b]	yield[c] (%)	ee (*trans*)[d] (%)
1	Et_3N	10	>98/<2	75	81
2	DMAP	10	>98/<2	65	93
3	CsF	10	98/2	54	83
4	DMF	10	>98/<2	77	84
5	H_2O	10	88/12	87	96
6[e]	H_2O	10	88/12	85	97
7	H_2O	5	88/12	74	76

[a]$CuPF_6$ = $Cu(CH_3CN)_4PF_6$. [b]Determined by ^{1}H NMR. [c]Isolated yield. [d]Determined by HPLC. [e]5 equiv of H_2O was used.

Scheme 2. Enantioselective [3 + 2] Cycloaddition of 1e−n with *N*-Phenylmaleimide



[a]Yield for isolated *trans* adduct. [b]Yield for the *trans*/*cis* mixture. [c]Determined by HPLC.

with 4-bromophenylmaleimide, was unequivocally established by X-ray diffraction.[17]

Gratifyingly, we found that silylimines with other heterocyclic substitution such as 2-quinolyl, 2-benzothiazolyl, and 2-thiazolyl proved also to be suitable partners in the cycloaddition affording the corresponding adducts with high yields, almost complete *trans* diastereoselectivity, and high enantioselectivity.

A screening of alternative dipolarophiles was next tested to explore the scope of this [3 + 2] cycloaddition. It was found

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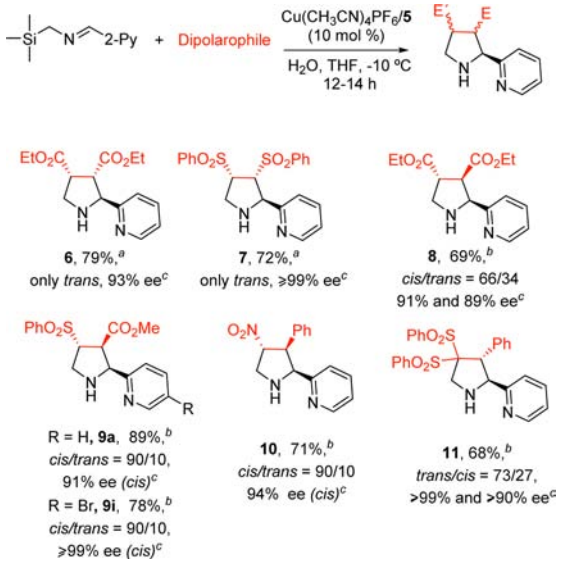
that acyclic *cis* symmetrically substituted diactivated alkenes (such as malonate and bisphenylsulfonyletylene) gave excellent results, affording the corresponding pyrrolidines with high diastereoselectivity and asymmetric induction (Scheme 3,

Scheme 3. Cycloaddition with Other Dipolarophiles



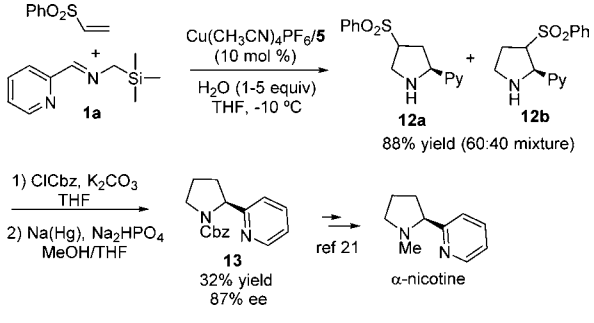
[a]Yield for isolated *trans* adduct. [b]Yield for the *trans/cis* mixture (*cis/trans* terminology with regard to C-2/C-3 substitution). [c]Determined by HPLC.

adducts **6** and **7**). In the cycloaddition with diethyl fumarate Walphos ligand **5** provided the pyrrolidine **8** with high enantioselectivity, albeit lower diastereoselectivity (*cis/trans* 66/34). The cycloaddition with *trans* unsymmetrically substituted alkenes such as 2-sulfonyl acrylate and nitrostyrene took place with complete regioselectivity[18] and high diastereoselectivity and enantioselectivity (Scheme 3, adducts **9** and **10**).

The stereochemical assignment of compound **9i** was unequivocally established by X-ray diffraction.[19] On the other hand, the cycloaddition of 1,1-(bis-sulfonyl)ethylene afforded a 73/27 mixture of *trans/cis* isomers with very high enantioselectivity (compound **11**).

Similarly, an excellent reactivity was observed in the cycloaddition with phenyl vinyl sulfone, providing a mixture of both regioisomers[20] **12a** and **12b** in 88% yield (Scheme 4). This mixture was directly transformed into the known α-nicotine precursor **13**[21] (87% ee) by protection of the nitrogen as Cbz and reductive sulfonyl elimination by treatment with

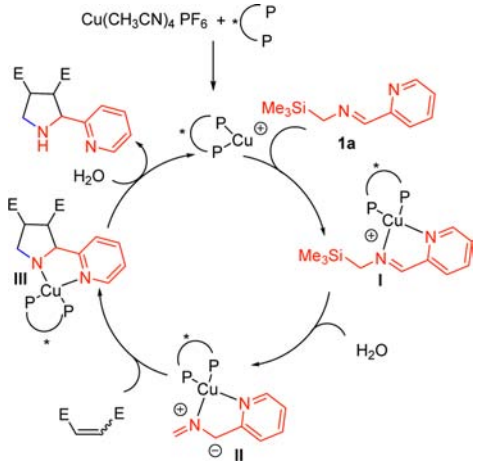
Scheme 4. Synthesis of α-Nicotine Precursor



Na(Hg), proving otherwise the absolute configuration at C-2 of the sulfonylated adducts **12**.

A simplified mechanistic hypothesis for the 1,3-dipolar cycloaddition is shown in Scheme 5. First, we observed that

Scheme 5. Mechanistic Hypothesis



no cycloaddition takes place under the optimal reaction conditions when phenyl-, 3-pyridyl-, or 4-pyridyl-substituted silylimines were used instead of **1a** (see the Supporting Information). These results suggest that the bidentate coordination of copper chiral complex with the silylimine **1a** is crucial for the activation of the substrate presumably to form the starting *N,N*-complex **I**. Next, water would facilitate the desylilation step leading to the key metalodipole **II**, which would undertake the cycloaddition with the dipolarophile to afford the metalated adduct **III**. Final protonation would provide the free pyrrolidine and the recovery of the copper catalyst.

In summary, a practical and efficient procedure for the direct enantioselective synthesis of α-heteroarylpyrrolidines, via [3 + 2] cycloaddition of heteroarylsilylimines with activated alkenes, has been developed. By use of $Cu(CH_3CN)_4PF_6$/Walphos **5** as the catalyst system, high enantioselectivity and moderate to high diastereoselectivity have been obtained with a wide variety of azomethine precursors and dipolarophiles.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data of **3k** and **9i**. Experimental procedures, characterization data for new compounds, and copies of NMR spectra and HPLC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information for details.

(16) **Typical procedure for the Asymmetric [3 + 2] Cycloaddition: (3a*S*,4*S*,6a*R*)-2-Phenyl-4-(2-pyridinyl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (3a).** To a solution of Walphos (15.8 mg, 17.10^{-3} mmol) and $Cu(CH_3CN)_4PF_6$ (6.3 mg, 17.10^{-3} mmol) in THF (0.5 mL), under nitrogen atmosphere, at −10 °C, were successively added water (3 μL, 0.17 mmol), a solution of *N*-phenylmaleimide (30.0 mg, 0.17 mmol) in THF (0.5 mL), and a solution of **1a** (50.0 mg, 0.26 mmol) in THF (0.5 mL). After 24 h at −10 °C, the mixture was diluted with dichloromethane and washed with ammonium hydroxide (3 × 5 mL) and brine (3 × 5 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (hexane−EtOAc 2:1) to afford a mixture (88:12) of the cycloadduct *trans*-**3a** and *cis*-**3a** (43.9 mg, 87%, colorless solid).

(17) Crystallographic data of **3k** are available in the Supporting Information.

(18) In other 1,3-dipolar cycloadditions of (*Z*) sulfonyl acrylates, the regioselectivity was also controlled by the sulfonyl group. See: López-Pérez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 340.

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(20) The structure of these regioisomers was established by ^{1}H NMR. See the Supporting Information for details.

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