Stereoselective Ag-catalyzed 1,3-Dipolar Cycloaddition of Activated Trifluoromethyl Substituted Azomethine Ylides

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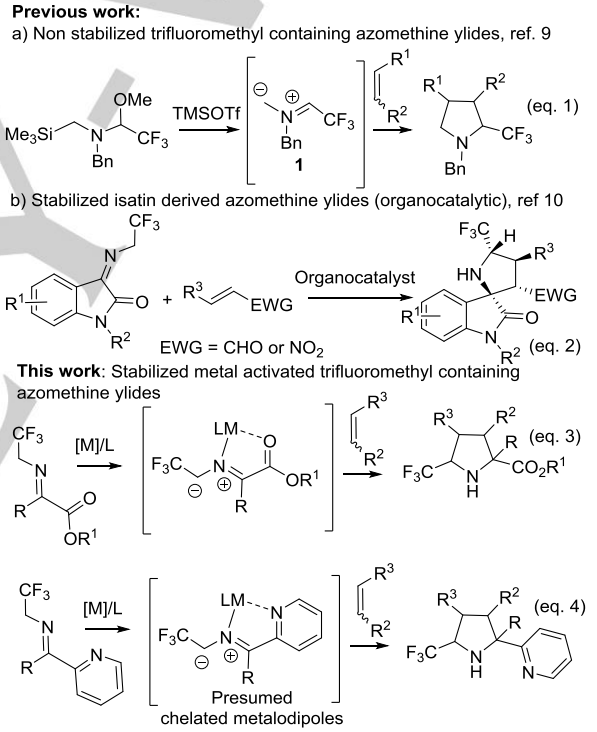
Dedicated to Prof. José Luis García Ruano on the occasion of his retirement.

Abstract: A silver catalyzed 1,3-dipolar cycloaddition of fluorinated azomethine ylides and activated olefins is reported. The reaction offers a straightforward and atom-economical procedure for the preparation of fluorinated pyrrolidines. Broad scope and high diastereoselectivities have been achieved simply using AgOAc/PPh_3 as catalyst system. The high efficiency of the cycloaddition relies on the presence of a metal coordinating group at the imine moiety, such as an ester moiety or an heteroaromatic ring. The asymmetric version of the cycloaddition has been developed using Taniaphos as chiral ligand.

Introduction

The pyrrolidine ring is a common component of pharmaceuticals as well as a highly valuable building block and organocatalyst in asymmetric synthesis.[1] In particular, modified proline derivatives have been extensively used to control the conformation of peptides for structure-activity relationship studies.[2] On the other hand, it is well documented that the replacement of hydrogen atoms by fluorine in organic compounds may result in a clear improvement of their biological properties.[3] For instance, the introduction of one or several fluorine atoms proximal to an amine moiety decreases the basicity, which can provide an improvement in the metabolic stability and lowering the toxicity.[4] Accordingly, the preparation of fluorinated pyrrolidine derivatives has attracted a growing interest. Nevertheless efficient methods for their stereoselective preparation based on the use of readily available starting materials are still scarce.[5]

Among the different approaches for pyrrolidine synthesis the catalytic 1,3-dipolar cycloaddition between azomethine ylides and activated alkenes has emerged as one of the most powerful.[6] Therefore, 3-trifluoromethylpyrrolidines have been efficiently prepared using trifluoromethylated alkenes as dipolarophiles, including several catalytic asymmetric examples.[7] However, the complementary approach based on the use of fluorinated azomethine ylide precursors for the synthesis of 2-trifluoromethylpyrrolidines has been seldom explored.[8] In this context an efficient procedure has been recently reported by Ley and co-workers[9] based on the in situ generation of the trifluoromethylated non-stabilized azomethine ylide **1** by reaction of a functionalized α-trimethylsilyl-α-alkoxyamine in the presence of a stoichiometric amount of a Lewis acid (Scheme 1, eq 1). In addition, concurrently with the development of our work, Wang and co-workers[10] have just reported the organocatalytic 1,3-dipolar cycloaddition of isatin derived trifluoromethylated azomethine ylides with enals or nitrostyrenes (Scheme 1, eq 2).



Scheme 1. Strategies for the preparation of 2-trifluoromethyl substituted pyrrolidines.

On the other hand, α-iminoesters such as glycinate esters are very common substrates in enantioselective 1,3-dipolar cycloadditions since they generate the corresponding azomethine species in the presence of a catalytic amount of a metal complex (frequently copper or silver chiral complexes) under very mild reaction conditions.[6] The great efficiency of this transformation relies on the formation of a rigid five membered metalated azomethine ylide which facilitates the deprotonation and further enantioselective cycloaddition.

On these grounds, we envisage that trifluoromethylated pyrrolidines could be prepared by cycloaddition of *N*-(2,2,2-trifluoroethyl) imines bearing a coordinating group such as

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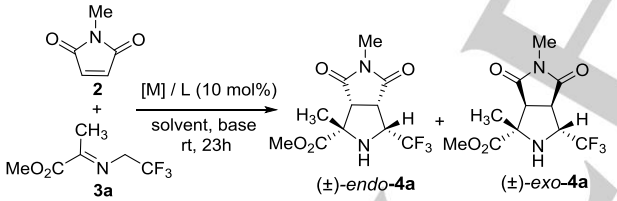
an ester (Scheme 1, eq 3) or a pyridyl unit (Scheme 1, eq 4) under metal-catalyzed reaction conditions. This protocol would provide access to 2-trifluoromethyl pyrrolidines with varied substitutions patterns and would pave the way for the development of the catalytic asymmetric procedure.

Results and Discussion

a) Optimization of the reaction conditions

At the outset of our studies we chose as model cycloaddition the reaction between *N*-methyl maleimide (**2**) and the trifluoromethyl substituted iminoester **3a,** readily prepared by condensation of 2,2,2-trifluoroethanamine with methyl pyruvate. To our delight, we observed that in the presence of a 10 mol% of a copper salt ($Cu(CH_3CN)_4PF_6$), PPh_3 as ligand and Et_3N as base, the pyrrolidine *endo*-**4a** was obtained in 50% yield and nearly complete diastereoselectivity (Table 1, entry 1). The yield could be significantly improved (70%) using AgOAc as metal source (entry 2). Other ligands such as dppe, dppf or (±)-BINAP were also found to promote the reaction albeit with less satisfactory results (entries 3-5). The next set of optimization experiments focused on the effect of bases and solvents. After screening a variety of combinations we found that the best results were obtained using *tert*-butyl methyl ether as solvent and Cs_2CO_3 (20 mol%) as base (entry 6). The reaction can be also performed using a lower catalyst loading (5 mol%) but resulting in a significant lower yield (entries 7 and 8). The relative configuration of the product *endo*-**4a** was determined by X-ray crystallographic analysis.[11]

Table 1. Reaction conditions optimization

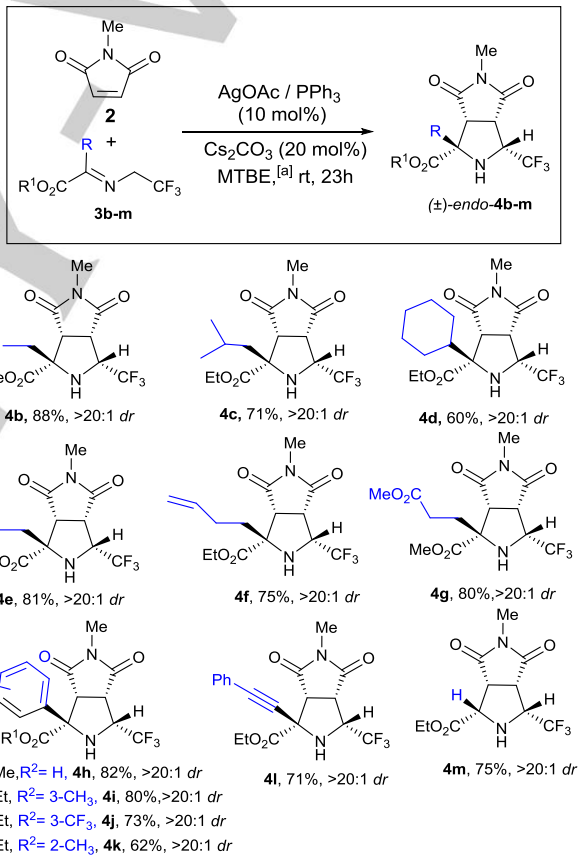


Entry	Metal salt	Ligand	Solvent	Base	Yield (%)[a]	dr (%)[b]
1	$CuPF_6$	PPh_3	THF	Et_3N	50	>20:1
2	AgOAc	PPh_3	THF	Et_3N	70	>20:1
3	AgOAc	dppe	THF	Et_3N	89	9:1
4	AgOAc	dppf	THF	Et_3N	93	9:1
5	AgOAc	(±)-BINAP	THF	Et_3N	66	>20:1
6	AgOAc	PPh_3	MTBE[e]	Cs_2CO_3	90	>20:1
7[c]	AgOAc	PPh_3	MTBE[e]	Cs_2CO_3	72	>20:1
8[d]	AgOAc	PPh_3	MTBE[e]	Cs_2CO_3	61	>20:1

[a] Isolated yield. [b] *endo*:*exo*, determined by ^{1}H-NMR in the crude reaction mixture. [c] 5 mol% of catalyst. [d] 3 mol% of catalyst. dppe = 1,2-Bis(diphenylphosphino)ethane. dppf = 1,2-Bis(diphenylphosphino)ferrocene. BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene. [e] MTBE: *tert*-butyl methyl ether.

b) Scope of the cycloaddition

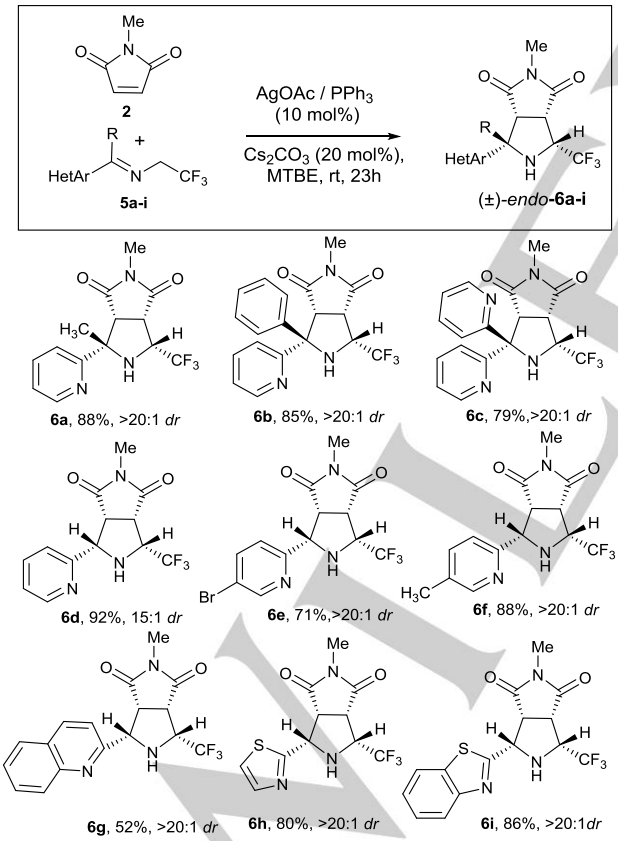
Upon completion of the optimization process, we examined the scope of the cycloaddition with a variety of trifluoromethyl substituted iminoesters **3b-m** (Scheme 2). The reaction proceeded efficiently regarding both the reactivity and diastereoselectivity with other alkyl substituents (products **4b-g**). The introduction of several functional groups on the side chain such as aryl, alkenyl or ester is also well tolerated (pyrrolidines **4e-g**). In the case of the sterically more demanding cyclohexyl substituted iminoester **3d** the cycloaddition also took place with very high diastereoselectivity, albeit with lower yield (**4d**, 60%). The catalytic system was similarly effective with aromatic substituted trifluoromethyl imines regardless of the substitution pattern at the arene (62%-82% yield, adducts **4h-k**). Alkynyl substituents are also well tolerated (adduct **4l**). Finally, the trifluoromethyl aldimine **3m**, derived from ethyl glyoxalate, was also a suitable substrate in this cycloaddition (75% yield, >20:1*dr*).



Scheme 2. Scope with regard to the azomethine ylide precursor. Yields of the isolated *endo* adduct; *dr* determined by ^{1}H-NMR in the crude reaction mixture [a] MTBE: *tert*-butyl methyl ether.

Next, further extension of the scope of the cycloaddition was focused on other types of potentially bidentate coordinating trifluoromethylated imines. In this regard, we envisaged that an heterocyclic moiety could act as coordinating group, in a similar manner that the ester moiety, promoting the 1,3-dipolar cycloaddition process.[12] To test the viability of this hypothesis, we first studied the

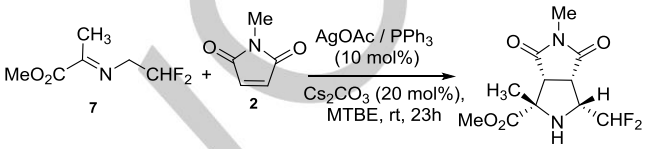
reaction between the imine **5a**, derived from 2-acetylpyridine, and *N*-methyl maleimide. Gratifyingly, under the previously optimized reaction conditions for the pyruvate-derived imines the reaction took place with high yield and almost complete diastereoselectivity (Scheme 3, adduct *endo*-**6a**). The introduction of an aromatic or heteroaromatic substituent at the imine moiety, instead of the methyl unit, had no significant influence on the reaction efficiency and diastereoselectivity (adducts **6b** and **6c**). The imine **5d,** derived from 2-pyridinecarboxaldehyde, also worked well affording the pyrrolidine *endo*-**6d** in 92% yield and high diastereoselectivity (15:1). A similar outcome was observed when imines **5e** and **5f**, having a substituted pyridyl unit, were engaged in the cycloaddition. Interestingly, azomethine precursors with varied heterocyclic substitution such as 2-quinolyl **5g**, 2- thiazolyl **5h** and 2-benzothiazolyl **5i** proved also to be suitable partners in the cycloaddition, affording the corresponding adducts with excellent *endo*-selectivity (adducts **6g-i**). In agreement with the necessity of using a bidentate-type trifluoromethylated imine having a suitably placed coordinating atom, no reaction was observed from the phenyl substituted imine, derived from benzaldehyde, under the optimized reaction conditions.[13]



Scheme 3. Heteroaryl substituted azomethine ylide precursors. Yields of the isolated *endo* adduct; *dr* determined by ^{1}H-NMR in the crude reaction mixture.

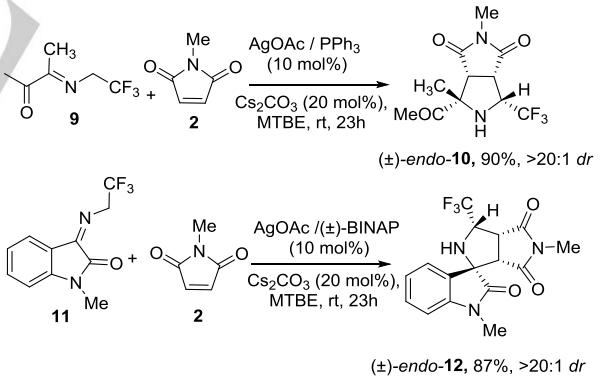
The introduction of a CF_2H moiety is also an interesting possibility in medicinal chemistry since this group can establish an additional hydrogen bond.[14] In addition, α-difluorinated amines are of particular interest because can be considered as lipophilic isosteres of β-aminoalcohols and therefore used in drug design.[15]

With this in mind, we next tested the extension of our methodology to the preparation of difluoromethylated pyrrolidines. To this end, difluoromethyl imine **7** was easily prepared from commercial available 2,2-difluoroethanamine and methyl pyruvate. Gratifyingly, the cycloaddition between imine **7** and *N*-methylmaleimide (**2**) under the optimized reaction conditions occurred with high yield and diastereoselectivity to provide *endo*-**8** (Scheme 4).



Scheme 4. [3+2] Cycloaddition of difluoromethyl azomethine ylide precursors.

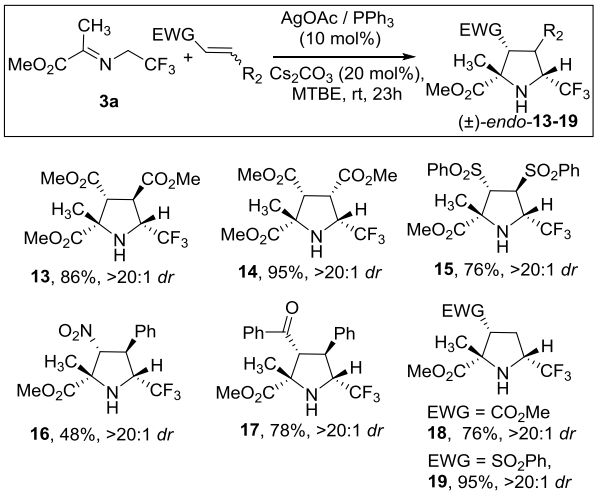
We also explored the behaviour of 2,3-butanedione derived imine **9** as azomethine ylide precursor. The reaction with maleimide **2** under standard conditions gave rise the corresponding pyrrolidine **10** in 90% yield and virtually complete endoselectivity. The reaction with the isatin derived cyclic imine **11**[10] took place with good yield albeit with very low diastereoselectivity. Pleasingly, when the cycloaddition was performed using (±)-BINAP as the ligand *endo*-adduct **12** was obtained as the only detectable product (Scheme 5).



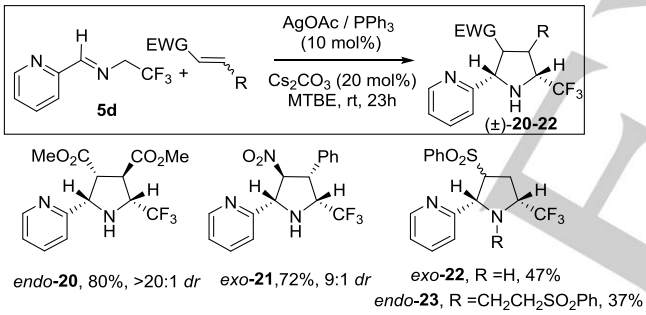
Scheme 5. 1,3-Dipolar cycloaddition of azomethine ylide precursors **9** and **11.**

In order to expand the substitution patterns at the pyrrolidine unit, we studied a diversity of dipolarophiles instead of the model *N*-methylmaleimide. We were pleased to find that a great variety of acyclic activated alkenes are suitable partners in the cycloaddition with imine **3a** (Scheme 6). Acyclic diactivated alkenes, such as dimethyl fumarate, maleate, or bissulfonylethylene proved to be excellent substrates in the reaction, affording the corresponding pyrrolidines **13-15** in high yield and diastereoselectivity. (*E*)-β-nitrostyrene and *trans*-chalcone also performed well although a moderate yield was

obtained in the former case (pyrrolidines **16** and **17**, 48% and 78% yield). Interestingly, monoactivated alkenes, such as methyl acrylate and phenyl vinyl sulfone also worked well affording the corresponding adducts with complete *endo* selectivity (pyrrolidines **18** and **19**). The relative stereochemistry of products *endo*-**15**, *endo*-**16** and *endo*-**19** was unequivocally established by X-ray crystallographic analysis.[16]



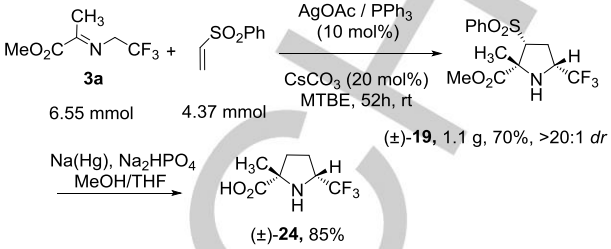
Scheme 6. Scope of dipolarophiles with activated imine **3a.** Isolated yields after chromatography; *dr* determined by ^{1}H-NMR in the crude reaction mixture.



Scheme 7. Scope of dipolarophiles with activated imine **5d**. Yields of the isolated major adduct; *dr* determined by ^{1}H-NMR in the crude reaction mixture

Similarly to the ester series the cycloaddition of the trifluoromethyl substituted imine **5d**, owning the coordinating 2-pyridyl unit, with dimethyl fumarate was also highly endoselective (Scheme 7, adduct **20**). In contrast, the reaction with (*E*)-β-nitrostyrene gave rise the *exo*-aduct **21** as major diastereomer. The use of phenyl vinyl sulfone as dipolarophile (2 equiv) led to a mixture of *endo/exo* isomers in which the *endo*-aduct underwent a subsequent aza-Michael reaction with phenyl vinyl sulfone to afford *endo*-**23** (Scheme 7). The relative configuration of the pyrrolidine *exo*-**22** was determined by X-ray crystallographic analysis.[17]

To highlight the usefulness of the method for the preparation of trifluoromethyl α-quaternary proline derivatives, we set out to test the scalability of the process. First, we performed a gram scale reaction between azomethine precursor **3a** and phenyl vinyl sulfone, providing *endo*-**19** in 70% (Scheme 8). Treatment of **19** with Na(Hg) led efficiently to the proline derivative **24** by reductive cleavage of the phenylsulfonyl group and hydrolysis of the methyl ester (85% yield, Scheme 8).



Scheme 8. Scale-up of the cycloaddition with phenyl vinyl sulfone and further desulfonylation.

c) Computational studies

In order to gain some insight into the reaction mechanism that could explain the different behavior of ester and pyridyl derived ylides in the reaction with monoactivated alkenes, such as phenyl vinyl sulfone, some theoretical studies by DFT calculations were carried out.[18] First, the structures and relative stability of the possible ylides complexes were explored (Figure 1).

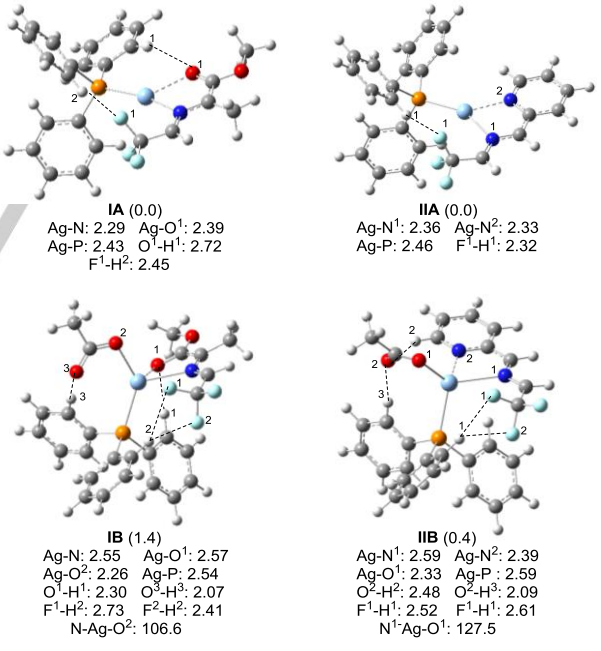
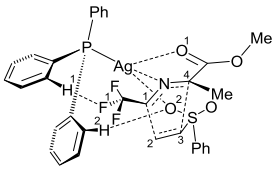


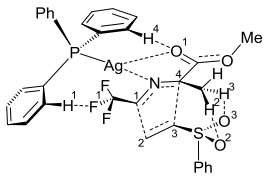
Figure 1. Optimized geometries of the possible ylide complexes derived from **3a** (**IA** and **IB**) and **5d** (**IIA** and **IIB**). Distances are given in Å. Calculated relative free energy at 298 K (kcal mol^{-1}) is indicated in parenthesis [SMD$_{THF}$/ M06 / 6-311+G(2df,2p) (C, H, N, O, F, P), LANL2TZ(f) (Ag) // B3LYP / 6-31G(d) (C, H, N, O, F, P), LANL2DZ(f) (Ag)].[18].

The structure of complexes with only one phosphine ligand was similar from both ylides (compare distances between the metal and the atoms coordinated for **IA** and **IIA**). However, when the coordination to an additional acetate

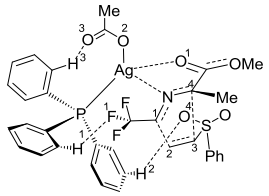
ligand was considered[19] the structures of the resulting complexes became quite different. Whereas in **IIB** the ligands around Ag atom show an almost trigonal pyramidal geometry, that could allow the approach of the alkene to one of the faces of the ylide without a significant steric hindrance, in the case of **IB** the ligands adopt an almost tetrahedral arrangement (compare N_{im}-Ag-O_{Ac} angle for both complexes) what would imply a higher steric hindrance during the approach of the alkene to both ylide faces.[20] In all cases, NBO analysis reveals the charge is mainly localized at the α position to CF_3 group, which is in agreement with the regioselectivity experimentally observed. Respect to the stability, the participation of both types of complexes, **A** and **B**, in the reaction cannot be discarded. Thus, the possible *endo* and *exo* transition states for each ylide in the reaction with phenyl vinyl sulfone were optimized (Figures 2 and 3).



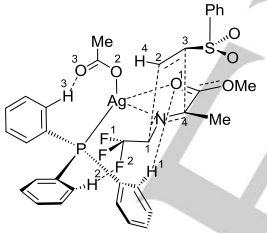
TSIA*endo* (16.3)
Ag-N: 2.35 Ag-O^1: 2.47
Ag-P: 2.45 Ag-O^2: 2.57
Ag-F^1: 2.89
C^1-C^2: 2.08 C^3-C^4: 2.89
F^1-H^1: 2.63 O^2-H^2: 2.45



TSIA*exo* (19.6)
Ag-N: 2.25 Ag-O^1: 2.47
Ag-P: 2.43 Ag-F^1: 2.91
C^1-C^2: 2.03 C^3-C^4: 2.86
F^1-H^1: 2.52 O^2-H^2: 2.55
O^1-H^4: 2.61 O^3-H^3: 2.65



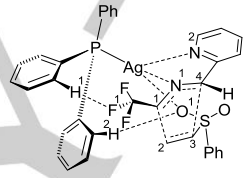
TSIB*endo* (19.0)
Ag-N: 2.65 Ag-O^1: 2.61
Ag-P: 2.48 Ag-O^2: 2.24
C^1-C^2: 2.22 C^3-C^4: 3.42
F^1-H^1: 2.55 O^3-H^3: 2.14
O^4-H^2: 2.39



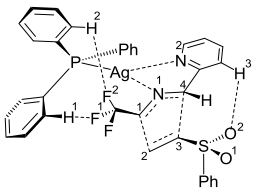
TSIB*exo* (19.1)
Ag-N: 2.56 Ag-O^1: 2.59
Ag-P: 2.52 Ag-F^1: 2.91
Ag-O^2: 2.26
C^1-C^2: 2.05 C^3-C^4: 3.21
O^1-H^1: 2.34 F^2-H^2: 2.52
O^3-H^3: 2.08 O^2-H^4: 2.40

Figure 2. Optimized geometries of the possible transition states involved in the reaction of **3a** with phenyl vinyl sulfone. Distances are given in Å. Calculated relative free energy at 298 K (kcal mol^{-1}) with respect to **IA** complex is indicated in parenthesis [SMD$_{THF}$ / M06 / 6-311+G(2df,2p) (C, H, N, O, F, P), LANL2TZ(f) (Ag) // B3LYP / 6-31G(d) (C, H, N, O, F, P), LANL2DZ(f) (Ag)].[18]

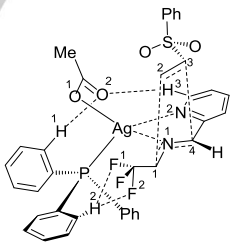
Figure 2 shows the possible transition states in the case of the ester derived ylide. **TSIA*endo***, that results from the *endo* approach to the most stable **IA** complex was also identified as the most stable one, about 3 kcal mol^{-1}, which is in agreement with the complete *endo*-selectivity observed. This higher stability is probably due to the strong stabilizing *endo* interaction between the silver atom and the sulfone group (*d*(Ag-O^2): 2.57 Å) that is not possible in the *exo* approach. Instead small contacts with methyl group were found (O^2-H^2; O^3-H^3). With respect to the reaction through **IB**, the most stable *endo* and *exo* transition states (**TSIB*endo*** and **TSIB*exo***), that in this case correspond to the approach of the alkene to opposite ylide faces,[18] were similar in energy since no additional stabilizing interactions were found. In the case of pyridyl derived ylide (figure 3), two transition states resulted to be more stable: **TSIIA*endo***, quite similar to that found for the analogous ester derivative, and **TSIIB*exo***, that shows less steric congestion than in the case of ester derivative thanks to the lack of the methyl group as well as the different coordination around the metal.[21] This situation could justify the low *endo/exo* selectivity found for **5d** in the reaction with this dipolarophile. According to the distances of the bonds that are being formed all of these transition states seem to be quite asynchronous and could correspond to a stepwise mechanism in which the first step consists of a Michael addition of the C_1 in the ylide to the vinyl sulfone to afford a zwiterionic intermediate that undergoes an intramolecular Mannich type reaction. All attempts to find this intermediate from **TSIIA*endo*** failed. However, from **TSIIB*exo***, both the zwiterionic intermediate as well as the corresponding Mannich type transition state could be located (1.6 and 5.6 kcalmol^{-1} respectively with respect to complex **IIA**, see SI for details).



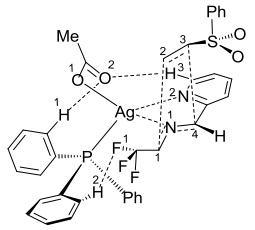
TSIIA*endo* (12.1)
Ag-N^1: 2.36 Ag-N^2: 2.43
Ag-P: 2.46 Ag-O^1: 2.63
Ag-F^1: 3.02
C^1-C^2: 2.24 C^3-C^4: 3.00
F^1-H^1: 2.35 O^1-H^2: 2.49



TSIIA*exo* (14.6)
Ag-N^1: 2.31 Ag-N^2: 2.38
Ag-P: 2.45 Ag-F^1: 3.07
C^1-C^2: 2.16 C^3-C^4: 2.83
F^1-H^1: 2.54 F^2-H^2: 2.46
O^2-H^3: 2.59



TSIIB*endo* (16.6)
Ag-N^1: 2.57 Ag-N^2: 2.41
Ag-P: 2.61 Ag-O^1: 2.32
C^1-C^2: 2.28 C^3-C^4: 3.33
F^1-H^2: 2.55 F^2-H^2: 2.64
O^2-H^1: 2.08 O^2-H^3: 2.43



TSIIB*exo* (12.8)
Ag-N^1: 2.55 Ag-N^2: 2.43
Ag-P: 2.58 Ag-O^1: 2.33
C^1-C^2: 2.28 C^3-C^4: 2.96
F^1-H^2: 2.50
O^2-H^1: 2.10 O^2-H^3: 2.43

Figure 3. Optimized geometries of the possible transition states involved in the reaction of **5d** with phenyl vinyl sulfone. Distances are given in Å. Calculated relative free energy at 298 K (kcal mol^{-1}) with respect to **IIA** complex is indicated in parenthesis [SMD$_{THF}$ / M06 / 6-311+G(2df,2p) (C, H, N, O, F, P), LANL2TZ(f) (Ag) // B3LYP / 6-31G(d) (C, H, N, O, F, P), LANL2DZ(f) (Ag)].[18]

In order to validate these models for pyridyl derived ylide in other reaction that takes place with complete *endo*-selectivity, transition states **TSIIA*endo*'** and **TSIIB*exo*'** resulting from the approach of *N*-methylmaleimide (instead of phenyl vinyl sulfone) to complex **IIA** and **IIB,** respectively, were studied (Figure 4). Both transition states seem to be

more synchronic than in the case of phenyl vinyl sulfone and their relative stability predicts an *endo/exo* ratio of 93:7 in good agreement with the experimental results.

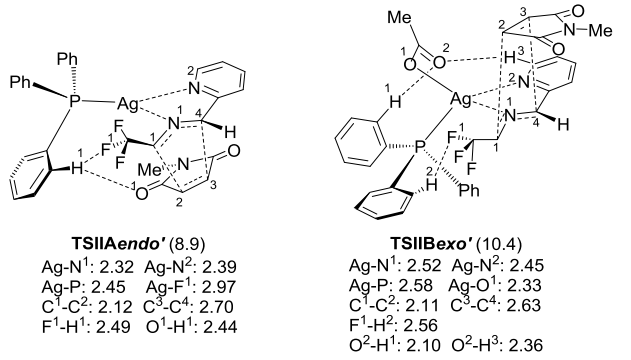


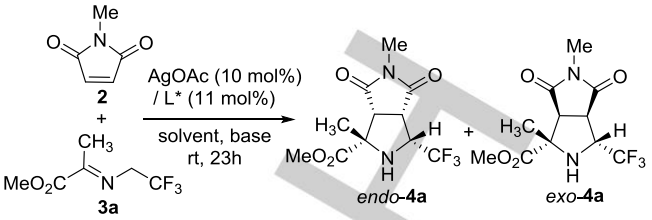
Figure 4. Optimized geometries of the possible *endo* and *exo* transition states involved in the reaction of **5d** with *N*-methylmaleimide. Distances are given in Å. Calculated relative free energy at 298 K (kcal mol^{-1}) with respect to **IIA** complex is indicated in parenthesis [SMD$_{THF}$ / M06 / 6-311+G(2df,2p) (C, H, N, O, F, P), LANL2TZ(f) (Ag) // B3LYP / 6-31G(d) (C, H, N, O, F, P), LANL2DZ(f) (Ag)].[18].

d) Development of the enantioselective [3+2] cycloaddition

Finally, we focused our efforts on developing the asymmetric variant of the cycloaddition. To achieve this purpose, several commercially available chiral ligands were tested in the reaction of **3a** with *N*-methylmaleimide (**2**) under Ag-catalyzed reaction conditions (Table 2). Very high diastereoselectivities but low enantioselectivities were observed with P,P axially chiral ligands, regardless of the phosphine substitution or the dihedral angle (entries 1-4). Among the tested ferrocenylphosphine ligands (entries 5-9), Taniaphos **L9** led to a significant improvement in the enantioselectivity (80% *ee*) but with low yield (32%, entry 9). Further optimization of the reaction conditions using Taniaphos **L9** ligand was then performed. Thus, after screening several solvents and bases the adduct *endo*-**4a** was obtained in 83% yield and 91% *ee* using AgOAc/**L9** as catalyst system in *tert*-butyl methyl ether as solvent in absence of base (entry 10). The catalyst loading could be reduced from 10 to 5 or 3 mol% with quite similar stereoselectivities albeit with a slightly lower isolated yield (entries 11 and 12).

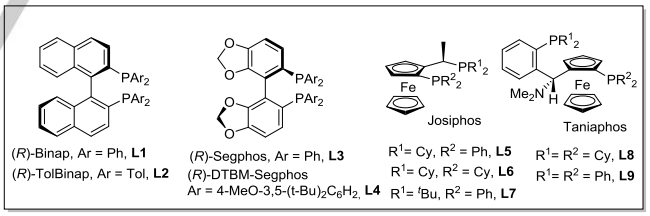
Under the optimized reaction conditions for the asymmetric protocol, other azomethine ylides were next studied. As showed in Scheme 9 the reaction worked well from alkyl substituted α-trifluoromethylmines giving rise the *endo* adducts with high yield, nearly complete diastereoselectivity, and excellent enantioselectivity (87-92% *ee*, pyrrolidines **4b,e,f**). In sharp contrast, no asymmetric induction was observed from the phenyl substituted imine **3h** (adduct **4h**).

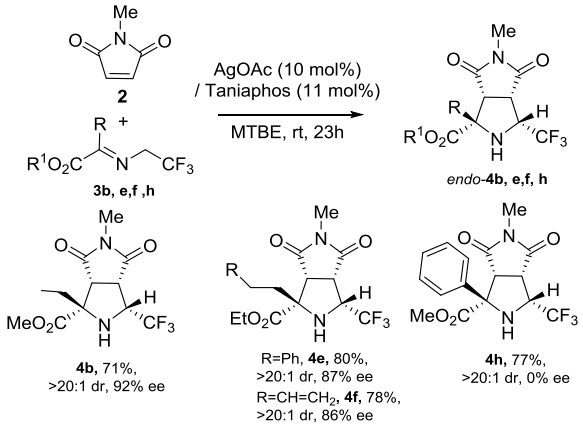
Table 2: Screening of ligands for the enantioselective 1,3-dipolar cycloaddition.



Entry	Ligand	Base	Solvent	Yield (%)[a]	*dr*[b]	*ee* (%)[c]
1	**L1**	Et_3N	THF	50	>20:1	30
2	**L2**	Et_3N	THF	47	>20:1	35
3	**L3**	Et_3N	THF	55	>20:1	25
4	**L4**	Et_3N	THF	61	>20:1	30
5	**L5**	Et_3N	THF	62	3:1	35
6	**L6**	Et_3N	THF	24	>20:1	0
7	**L7**	Et_3N	THF	30	>20:1	0
8	**L8**	Et_3N	THF	19	>20:1	50
9	**L9**	Et_3N	THF	32	>20:1	80
10	**L9**	--	MTBE	83	>20:1	91
11[d]	**L9**	--	MTBE	74	>20:1	92
12[e]	**L9**	--	MTBE	72	>20:1	92

[a] In pure adduct *endo*-**4a** after column chromatography [b]. Determined by ^{1}H NMR from the crude reaction mixtures. [c] By HPLC, see Supporting Information for details. [d] 5 mol% of AgOAc and 6 mol% of **L9** were used. [e] 3 mol% of AgOAc and 4 mol% of **L9** were used.





Scheme 9. Scope of the asymmetric cycloaddition.

The observed enantioselectivity can be rationalized on the basis of the structure of the possible ylide complexes with **L9**. The most stable **IC** complex (Figure 5) shows a less steric hindrance for the approach of the dipolarophile through the (2*Si*, 4*Re*) face that would afford the major enantiomer experimentally observed.[22]

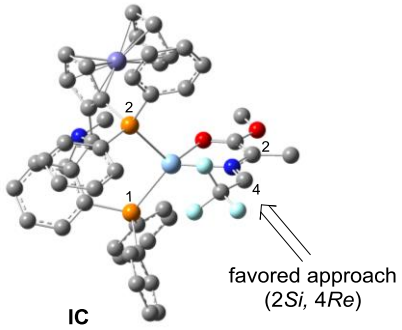


Figure 5. Optimized geometry of the presumed most stable ylide complex derived from **3a** and **L9**.[18] Hydrogen atoms have been removed for clarity.

Conclusions

In summary, we have developed an efficient method for the preparation of β-trifluoromethyl (and β-difluoromethyl) pyrrolidines by Ag-catalyzed 1,3-dipolar cycloaddition of fluorinated azomethine ylides with a variety of olefins. Very high diastereoselectivities (typically *endo*) are obtained using the simple AgOAc/PPh_3 catalyst system. The high reactivity of this protocol strongly relies on the presence of a metal coordinating ester group or heteroaryl unit at the imine, which promote the in situ formation of the azomethine ylide. Examples of the catalytic asymmetric version of this cycloaddition using Taniaphos as chiral ligand have been also developed.

Experimental Section

Experimental Details.

Acknowledgements

Financial support of this work by the *Ministerio de Economía y Competitividad* (MINECO, CTQ2012-35790) is gratefully acknowledged. A. P. thanks the *Ministerio de Educación y Ciencia* (MEC) for a predoctoral contract. We thank Takasago Company (Dr. Taichiro Touge) for generous loans of Segphos chiral ligands. We also thank the Centro de Computación Científica (UAM) for generous allocation of computer time.

Keywords: 1,3-dipolar cycloaddition • fluorinated pyrrolidines • silver • azomethine ylide • asymmetric catalysis

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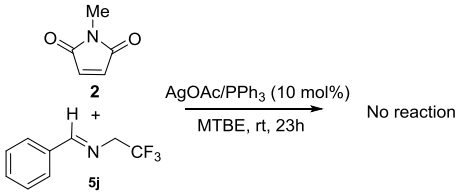
[13] The phenyl imine **5j** proved to be completely unreactive.



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[17] CCDC 1437444 contains the supplementary crystallographic data for compound *exo*-**22**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

[18] See SI for details.

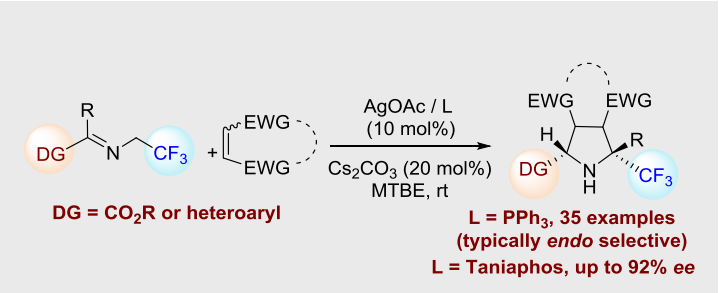
[19] The importance of the counterion on the *endo/exo*-selectivity of 1,3-dipolar cycloadditions between azomethine ylides and nitroalkenes had been observed and supported by theoretical calculations that included the OTf fragment (L. M. Castelló, C. Nájera, J. M. Sansano, O. Larrañaga, A. de Cózar, F. P. Cossío, *Adv. Synth. Catal*. **2014**, *356*, 3861). The coordination of an additional phosphine ligand was also considered. Although the resulting complex was more stable (-3.5 kcal mol^{-1}) the corresponding *endo* transition state derived from the approach of phenyl vinyl sulfone resulted somewhat less stable (17.4 kcal mol^{-1} respect to **IA**. See SI for details and structures **ID** and **TSID*endo***).

[20] A more pyramidal complex could be obtained from **IB** by changing the conformation of phosphine ligand. However, the complex itself as well as the corresponding *exo* transition state, derived from the approach of phenyl vinyl sulfone to the less hindered face, were less stable (3.9 and 19.3 kcal mol^{-1} respectively respect to **IA**. See SI, structures **IB'** and **TSIB'*exo***).

[21] In **TSIB*exo***, the presence of OAc determines a variation of the arrangement of the vinyl sulfone moiety (compare to **TSIA*exo***). The distance S-C_{Me} (3.59 Å) is close to the sum of van der Vaals radii (3.50 Å). To avoid this interaction both dihedral angle CF_3-C_1-C_2-C_3 as well as C_3-C_4 distance increase respect **TSIIB*exo*** decreasing the electrostatic stabilization between the developing charges located at C_3 and C_4.

[22] Another complex with the opposite arrangement of the ylide moiety (CF_3 group directed towards the ferrocenyl rings in the chiral ligand) resulted to be less stable (3.2 kcal mol^{-1} with respect to **IC**) and with a poorer steric differenciation of ylide faces (see SI, structure **IC'**). In **IC**, the angle between the ylide plane (defined by C_2, C_4 and Ag atom) and that defined by the closest hydrogen atoms to ylide on Ph group bonded to P_2, ferrocenyl group and Ag atom (that relates to the steric hindrance through the upper 2*Re*, 4*Si* face) is 68.7º. However, the angle between the ylide plane and that defined by the closest hydrogen atoms to ylide on Ph groups bonded to P_1 and Ag atom (that relates to the steric hindrance through the lower 2*Si*, 4*Re* face) is 89.1º. In the case of the reaction of **3h**, the phenyl group on C2 adopts conformations out of the ylide plane increasing steric hindrance through both faces (see SI, structures **IIIDa** and **IIIDb**) which could explain the lack of asymmetric induction.

FULL PAPER



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Stereoselective Ag-catalyzed 1,3-Dipolar Cycloaddition of Activated Trifluoromethyl Substituted Azomethine Ylides

A silver catalyzed efficient 1,3-dipolar cycloaddition of fluorinated azomethine ylides with activated olefins has been reported. A wide variety of fluorinated pyrrolidines were obtained under simple reaction conditions with high yields and diastereoselectivities. The enantioselective cycloaddition could be achieved in the presence of a Taniaphos chiral ligand to afford the corresponding adducts with high enantioselectivity (up to 92% *ee*). The high reactivity observed in the cycloaddition relies on the presence of a metal coordinating moiety, such as an ester or an heteroaryl group, at the azomethine ylide precursor. Theoretical studies by DFT calculations were carried out in other to gain some insight into the stereochemical outcome.