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This is an **author produced version** of a paper published in:

Chemical Communications 58.56 (2022): 7805-7808

DOI: <https://doi.org/10.1039/d2cc02902b>

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COMMUNICATION

Catalytic Enantioselective Intramolecular 1,3-Dipolar Cycloaddition of Azomethine Ylides with Fluorinated Dipolarophiles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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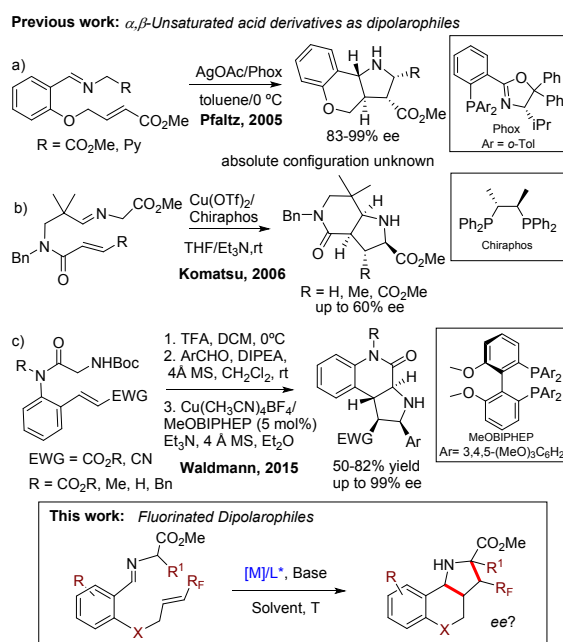
An enantioselective synthesis of polycyclic fluorinated pyrrolidines has been achieved by Cu-catalyzed intramolecular 1,3-dipolar cycloaddition of azomethine ylides with fluorinated dipolarophiles. The method displays a wide scope and afforded the desired cycloadducts in high yields with up to 99% *ee*. These results demonstrate that fluoroalkyl substituents are excellent activating groups in this transformation.

The 1,3-dipolar cycloaddition of azomethine ylides is undoubtedly one of the most useful, regio- and stereocontrolled methodologies for the synthesis of differently substituted pyrrolidines, with the generation of up to four new chiral centers.¹ The intramolecular version allows for the formation of fused pyrrolidines, which has been broadly studied and used for the preparation of pyrrolidine or pyrrol containing polycyclic natural products.²

Over the past two decades a great effort has been focused on the catalytic asymmetric intermolecular version of this [3+2] cycloaddition. As result, a pool of efficient catalytic systems, which enabled the improvement of the structural scope of the reaction (initially limited to the use of highly activated olefins) has been developed.³ However, by comparison, the catalytic asymmetric intramolecular cycloaddition remains underdeveloped. In fact, as far as we are aware, only four examples of this transformation have been described. The first was reported by Pfaltz in 2005, using Ag^I/PHOX as catalytic system for the preparation of a variety of hexahydrocromenopyrrolidines with excellent diastereo- and enantioselectivities (Scheme 1a).⁴ Subsequently, Komatsu and co-workers reported the cycloaddition of a range of α,β -

unsaturated amides using the Cu^{II}/Chiraphos complex as catalyst, although with moderate enantioselectivities (Scheme 1b).⁵ In 2014 Waldmann described an expeditious synthesis of enantioenriched pyrrolidino-piperidines by Cu^I/MeOBIPHEP catalyzed intramolecular cycloaddition of azomethine ylides (Scheme 1c).⁶ In addition, an organocatalytic cycloaddition was described by Gong and co-workers in 2010.⁷

Scheme 1: Metal catalyzed asymmetric intramolecular 1,3-dipolar cycloadditions. Previous work and working hypothesis.



On the other hand, due to its biological relevance, the enantioselective preparation of fluorinated pyrrolidines has generated a singular interest.⁸ Among the existing procedures for their preparation, the catalytic asymmetric intermolecular 1,3-dipolar cycloaddition of azomethine ylides and fluorinated dipolarophiles has emerged as one of the most appealing. Nevertheless, the dipolarophiles used to the date, required the presence of an extra activating group such as ester, nitro, or sulfone.⁹ In 2019, our research group reported an

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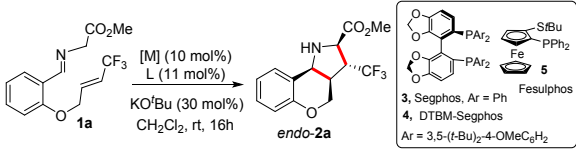
† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization. For ESI see DOI: 10.1039/x0xx00000x

intramolecular 1,3-dipolar cycloaddition between homoquiral morpholinone derived azomethine ylides and CF₃ substituted alkenes.¹⁰ After an oxidative deprotection step the corresponding polycyclic proline derivatives were obtained with high levels of regio and diastereoselectivity.

Based on our previous experience in this field,^{10,11} we envisaged that a metal-catalyzed intramolecular 1,3-dipolar cycloaddition of azomethine ylides with CF₃-substituted dipolarophiles could offer an expedite route to enantioenriched fluorinated polycyclic proline-derivatives which potential biological interest.⁸

At the outset of our studies, we chose the iminoester **1a** (readily prepared by condensation of methyl glycinate and the required fluorinated benzaldehyde and used without further purification)¹⁰ as model substrate. Under the conditions frequently used by our research group in the intermolecular reaction¹¹ (Cu(CH₃CN)₄ as metal source, (*R*)-Segphos **3** as ligand, and Et₃N as base in CH₂Cl₂) no cycloaddition was observed (entry 1, Table 1). In contrast, the anticipated cycloadduct **2** was obtained with high conversion, excellent diastereocontrol (only the *endo* isomer was observed by ¹H-NMR) and enantiocontrol (93% *ee*) when KO^tBu was used as base (entry 2). Lower yield and enantioselectivity was observed in the presence of AgOAc as metal source (entry 3). The use of THF or toluene as solvents led to poorer results (entries 4 and 5). The reaction performed with a lower catalyst loading (5 mol %) resulted in a significant lower yield but preserving the enantiomeric excess (entry 6). Other ligands commonly used in this reaction revealed that no cycloaddition was observed with the bulkier DTBM-Segphos ligand (**4**) (entry 7) while a 70% yield and 75% *ee* was obtained using Fesulphos (**5**) (entry 8).

Table 1. Optimization of reaction conditions for **1a**.



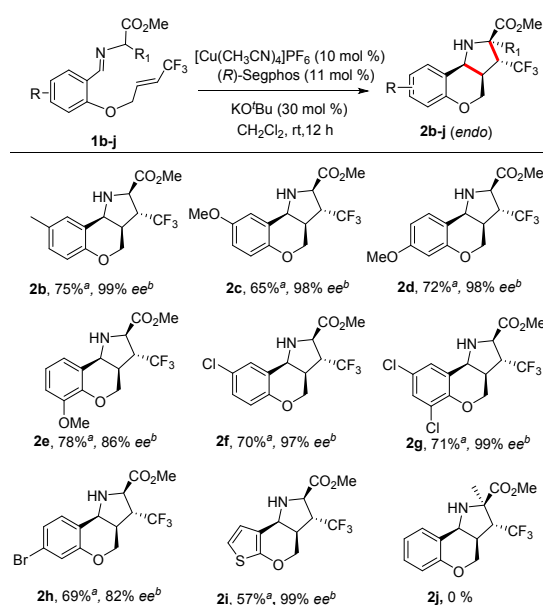
| Entry | [M] | L* | base | solvent | Yield (%) ^b | <i>ee</i> (%) ^c |
|-------|--------------------------------------|----------|--------------------|---------------------------------|------------------------|----------------------------|
| 1 | CuPF ₆ ^[a] | 3 | Et ₃ N | CH ₂ Cl ₂ | 0 | -- |
| 2 | CuPF ₆ ^[a] | 3 | KO ^t Bu | CH ₂ Cl ₂ | 80 | 93 |
| 3 | AgOAc | 3 | KO ^t Bu | CH ₂ Cl ₂ | 67 | 79 |
| 4 | CuPF ₆ ^[a] | 3 | KO ^t Bu | THF | 10 | -- |
| 5 | CuPF ₆ ^[a] | 3 | KO ^t Bu | toluen e | 65 | 24 |
| 6 | CuPF ₆ ^{[a],[d]} | 3 | KO ^t Bu | CH ₂ Cl ₂ | 46 | 93 |
| 7 | CuPF ₆ ^[a] | 4 | KO ^t Bu | CH ₂ Cl ₂ | -- | -- |
| 8 | CuPF ₆ ^[a] | 5 | KO ^t Bu | CH ₂ Cl ₂ | 70 | 75 |

^aCu(CH₃CN)₄PF₆. ^bIsolated yield after chromatographic purification. ^c*ee* determined by HPLC. ^d5 mol% of catalyst.

With this optimal reaction conditions in hand, we next studied the scope of the reaction. As shown in scheme 1, electronically diverse substituents at different positions of the aromatic ring of the azomethine ylide precursors were well tolerated. Thus,

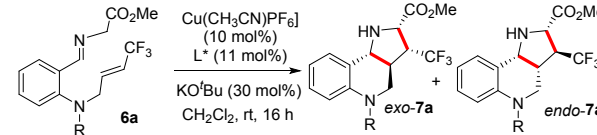
iminoesters with electron donating substituents, such as methyl or methoxy (**2b-e**), proved to be excellent substrates in this transformation affording the corresponding *endo*-adducts with almost complete diastereoselectivities, high yields and enantioselectivities. Excellent results were also obtained with halogenated iminoesters **1f-h**. Interestingly, thiophenyl derivative **1i** also underwent the cycloaddition providing the corresponding adduct **2i** with high yield and enantioselectivity. In contrast, no cycloaddition was observed with alanine based iminoester **1j** (Scheme 2). The relative and absolute configuration of the cycloadducts was unambiguously determined by X-ray crystal structure analysis of **2g**.¹²

Scheme 1: Scope of the reaction

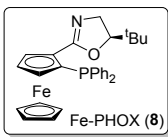


^aIsolated yield after chromatographic purification. ^b*ee* determined by HPLC.

We next evaluated the effect of changing the nature of the linker (X) between the dipolarophile and the aromatic ring. The use of iminoester **6a** (X = NTs) under optimized conditions resulted in full conversion but a drop of diastereoselectivity and enantioselectivity was observed (60% *dr*, 10% *ee*, Table 2, entry 1). Interestingly, an inversion in the diastereoselectivity was observed with the formation of the *exo*-adduct **7a** as major product.¹³ Almost complete diastereoselectivity but unsatisfactory levels of enantioselectivity were achieved using Fesulphos ligand **5** (entry 2). Similar results were also obtained with N-mesyl substrate (entry 3). Pleasingly, using Fe-PHOX (**8**) the reaction took place with similar yield (63%), excellent *exo*-diastereoselectivity and improved enantiocontrol (85% *ee*, entry 4). Then, we turned to explore the scope of the cycloaddition with regard to N-tosyl iminoesters **6** (Scheme 2). We were pleased to observe that Fe-PHOX (**8**)/Cu^I complex effectively catalyzed the reaction independently of the electronic character of the substituents at the aromatic ring (Scheme 2, adducts **7b-c**). Modify the number of fluorine atoms present in a molecule is a useful tool in medicinal chemistry for adjusting critical properties such as metabolic stability.

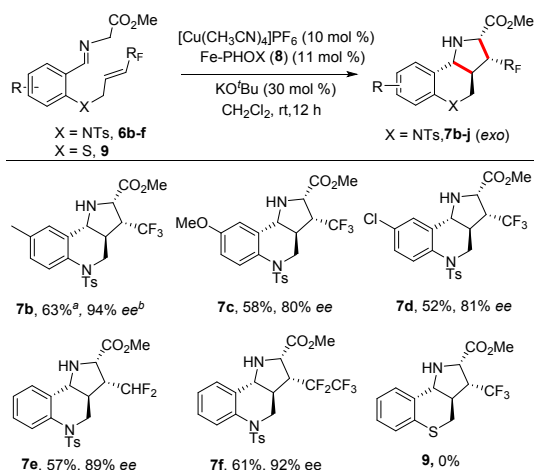
Table 2. Optimization of the reaction conditions for sulfonamide iminoesters


| Entry | R | L* | Exo/endo | Yield (%) ^a | ee (%) ^b |
|-------|----|----------|----------|------------------------|---------------------|
| 1 | Ts | 3 | 80/20 | 41 | 10 ^c |
| 2 | Ts | 5 | >99/<1 | 47 | 38 ^c |
| 3 | Ms | 5 | >99/<1 | 20 | 7 ^c |
| 4 | Ts | 8 | >99/<1 | 63 | 85 |



^aIsolated yield after chromatographic purification. ^bee determined by HPLC. ^cThe opposite enantiomer was obtained.

In this vein, we next tested the possibility of applying this methodology to the preparation of difluoromethylated and polyfluorinated heterocycles. Gratifyingly, the cycloadditions of iminoesters **6e** and **6f** under the optimized reaction conditions took place with good yield and enantioselectivity to provide the desired products **exo-7e-f**. In contrast, the formation of cycloadduct **9** with a sulfur atom in its structure was not observed in any of the conditions tested.

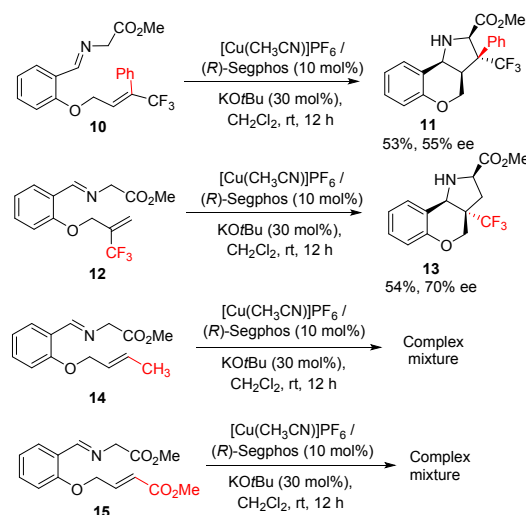
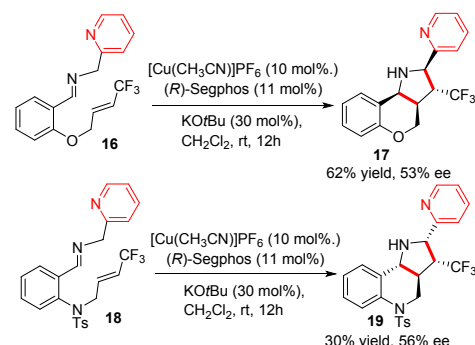
Scheme 2: Scope of 1,3-dipolar cycloaddition of N-tosyl derivatives

^aIsolated yield after chromatographic purification. ^bee determined by HPLC.

We next study the effect of the substitution at the alkene in the cycloaddition. Substrate **10** with a trisubstituted olefin led to the corresponding adduct **11** with acceptable yield (53%) but lower enantioselectivity (55% ee). Interestingly, the reaction also occurred with iminoester **12** with the trifluoromethyl group located at the non-terminal carbon atom, which afforded the corresponding hexahydrocromepyrrole **13** bearing a trifluoromethylated quaternary stereocenter, with moderate yield and enantioselectivity (54% yield, 70% ee). Nevertheless, a complex reaction mixture was obtained when non fluorinated iminoester **14**, in which the CF₃ group has been substituted by a methyl group, was subjected to the optimized reaction conditions. Unexpectedly, in contrast to the results obtained by Pfaltz in the silver catalyzed cycloaddition,⁴ no reaction was observed when α,β-unsaturated

ester **15** was used in the reaction. These results would indicate that the trifluoromethyl group plays a crucial role in the reactivity and selectivity of the process.

The reaction is not limited to the use of iminoesters as azomethine ylide precursors, substrates **16** and **18** with a pyridine ring instead an ester group also proved to be suitable dipole precursors in this cycloaddition although lower enantioselectivities were observed (**17**, 53% ee and **19**, 56% ee, Scheme 4).

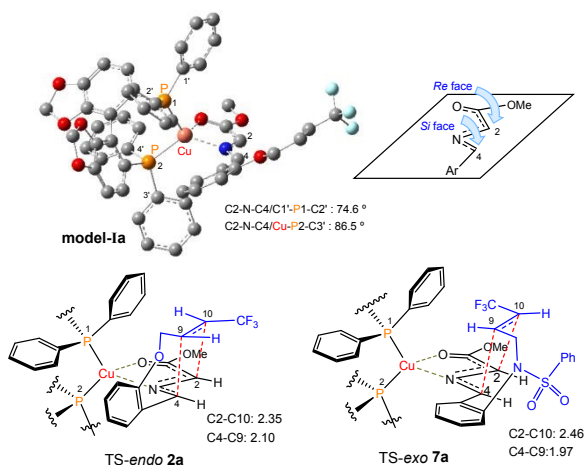
Scheme 3: Effect of the substitution at the alkene**Scheme 4:** Reaction of iminomethylpyridines

To gain further understanding of the stereochemical control of the process, the possible intermediates of the model reaction of substrate **1a** using **3** as a ligand were studied by DFT calculations.¹⁴ Figure 1 shows the structure of **mod-1a**, the most stable complex found from the ylide derived from **1a**, Cu(I) and ligand **3**. There is a clear difference in steric hindrance between both faces of the ylide. Whereas in the upper (2*Re*, 4*Si*) face the angle between the planes defined by the ylide and the phenyl rings bound to P1 allows to reach the conformation required for the reaction that yield the major product **endo-2a** (less sterically hindered approach with the CF₃ group far from the Ph ring of the ligand), the equivalent approach through the other face is much more hindered since one of the Ph groups bound to P2 points towards N atom (perpendicular arrangement between the ylide plane and that defined by Cu-P2-C3'). From this model, the optimized structures of the

corresponding transition states predict a 94 % *ee* in excellent agreement with the experimental result. According to these computational studies the inclusion of a molecule of ROH (from the base) forming a hydrogen bond with the ether linker of the substrate would contribute to explain the very high *endo*-selectivity.¹⁵ The inversion of diastereoselectivity observed in the case of **6a**, in which the NTs group cannot be involved in similar interactions, supports this hypothesis. In fact, Ts group directed towards Ph groups bound to P1, might be responsible for the destabilization of the *endo* approach to give mainly the *exo* product through **TS-*exo*7a**. On the other hand, by changing the CF₃ into a Me group, the barrier for the cycloaddition significantly increased (from 15.5 to 24.2 kcal·mol⁻¹) in agreement with the outstanding activating effect of the CF₃ group.

In conclusion, we have developed a catalytic asymmetric intramolecular 1,3-dipolar cycloaddition of azomethine ylides using fluorinated dipolarophiles. The structure of the linker connecting the dipole and dipolarophile is crucial to the diastereoselectivity. Oxygenated iminoesters **1** selectively gave rise the *endo* adducts when Cu/Segphos (**3**) complex was used as catalyst. Cu/Fe-PHOX (**8**) effectively catalyzed the reaction of N-tosyl iminoesters **6** affording the *exo*-adducts with high diastereo and enantioselectivity. Theoretical calculations properly explain this inversion of the diastereoselectivity.

Figure 1: Optimized geometry of **mod1a** (hydrogen atoms have been omitted for clarity) and simplified representation of the most stable transition states that lead to *endo*-**2a** and *exo*-**7a** (a simplified PhSO₂ was used instead of Ts). Relevant distances (Å) angles between planes (°) are indicated.



(M06/6-311++G(d,p) (C,H,N,O,P,F), LANL2TZ(f) (Cu)/SMD(CH₂Cl₂)/B3LYP-D3/6-31G(d) (C,H,N,O,P,F), LANL2DZ(f) (Cu)).

We thank FEDER/Ministerio de Ciencia, Innovación y Universidades Agencia Estatal de Investigación (Grants PGC2018-098660-BI00, PID2020-115294GB-I00 and PID2020-113059GB-C22) for financial support. C. C. thanks CAM for a research contract (PEG-2020-AI/IND-18195) and D. G. thanks the Spanish Ministerio de Educación, Cultura y Deporte for a predoctoral fellowship (FPU18/02750). We thank the Centro de Computación Científica at the UAM for their generous allocation of computer time.

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- CCDC 2173558 contains the supplementary crystallographic data www.ccdc.cam.ac.uk/data_request/cif. It is important to point out that the protocol reported in ref. 10, using a chiral azomethine ylide, led to the formation of the epimers of compound **2** at the carbon-2 of the pyrrolidine being therefore a complementary methodology.
- The relative and absolute configuration of the N-tosylated cycloadducts was determined by X-ray diffraction analysis of **7b**. CCDC 2173555 contains the supplementary crystallographic data www.ccdc.cam.ac.uk/data_request/cif.
- See Supporting Information for details.
- The optimized structures of transition states to yield *endo*-**2a** and *exo*-**2a** through the less hindered ylide face (2*Re*,4*Si*) predicted a diastereoselectivity (*endo*/*exo* = 80/20) in absence of the coordinating alcohol and (*endo*/*exo* = 99/1) in the presence of a MeOH molecule, as a model for *t*BuOH, see SI for the complete DFT study.