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Cu^{I}-Catalyzed Asymmetric [3 + 2] Cycloaddition of Azomethine Ylides with Cyclobutenones

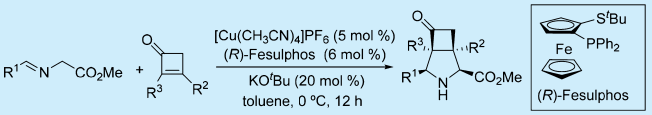
Javier Corpas,[†,§] Alberto Ponce,[†,§] Javier Adrio,*[,†,‡] and Juan C. Carretero*[,†,‡]

[†]Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

[‡]Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain

Supporting Information

ABSTRACT: The catalytic asymmetric 1,3-dipolar cycloaddition of cyclobutenones with azomethine ylides provides straightforward access to densely substituted 3-azabicyclo[3.2.0]heptanes. In the presence of Cu^{I}/(R)-Fesulphos as the catalytic system, high levels of diastereoselectivity and enantioselectivity were achieved (up to 98% enantiomeric excess (ee)).



The availability of efficient procedures for the straightforward preparation of substituted pyrrolidines is an important issue in synthetic and medicinal chemistry, since this heterocyclic unit is a key component in numerous biologically active compounds and catalysts.[1] In particular, 3-azabicyclo[3.2.0]heptanes derivatives shown interesting biological properties are receiving growing interest in drug discovery, because of their use as conformationally constrained surrogates for the piperidine ring[2] (see Figure 1). However, the lack of efficient synthetic procedures for the enantioselective preparation of azabicycloheptanes has limited their applicability.[3]

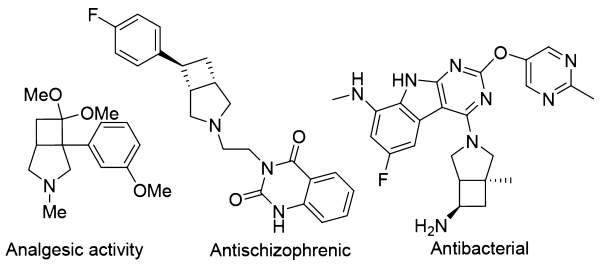
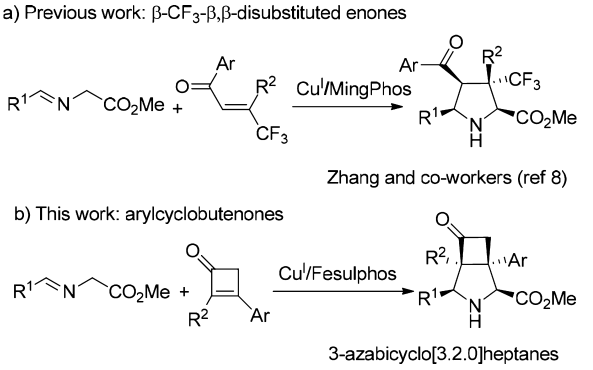


Figure 1. Biologically active 3-azabicyclo[3.2.0]-heptanes.

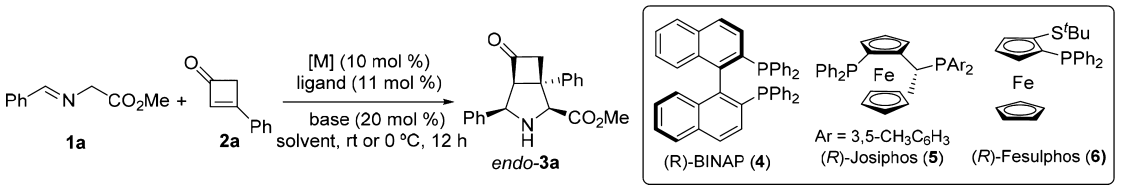
In the last two decades, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with activated olefins has become a privileged strategy within the synthetic chemists' toolbox for the enantioselective synthesis of pyrrolidines.[4] The impressive effort devoted in this field to develop new catalytic systems has greatly facilitated expansion of the structural scope with regard to both reaction partners.[5] In this context, α,β-unsaturated enones have emerged as one of the most useful dipolarophiles in this catalytic asymmetric transformation. Since the first report by our research group in 2009,[6] a wide range of suitable enones has been studied.[7] However, the use of β,β-disubstituted enones, which would enable the preparation of pyrrolidines with a quaternary stereocenter at the C_3 position, remains particularly challenging, because of the high sensitivity of the reaction to steric effects at the dipolarophile. Very recently, Zhang and co-workers have described access to enantioenriched pyrrolidines bearing a quaternary stereocenter at C_3 by a copper(I)-catalyzed [3 + 2] cycloaddition of azomethine ylides with β-CF_3-β,β-substituted enones (Scheme 1, eq 1).[8] In contrast, to the best of our knowledge, tetrasubstituted or β,β-disubstituted enones lacking an electron-withdrawing group in the beta position have not been reported so far.

Scheme 1. β,β-Disubstituted Enones as Dipolarophiles in Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides



On the other hand, cyclobutenones have proven to be excellent dipolarophiles in Diels–Alder reactions, because of their ring strain, which makes the reaction much more favorable than in the case of cyclopentenones or cyclohexenones.[9] As far as we are aware, the use of cyclobutenones as dipolarophiles in enantioselective 1,3-dipolar cycloadditions of azomethine ylides has not been previously reported. Taking advantage of the ring strain of the cyclobutenone moiety, we envisaged that sterically

Table 1. Optimization of the Reaction Conditions



entry	[M]	solvent	base	ligand	yield[a] (%)	*endo*/*exo*[b]	ee[c] (%)
1	AgOAc	THF	Et_3N	(±)-binap (**4**)			
2	$Cu(CH_3CN)_4PF_6$	THF	Et_3N	(±)-binap (**4**)			
3	AgOAc	THF	KHMDS	(±)-binap (**4**)	53	>98:2	
4	AgOAc	THF	KO^{t}Bu	(±)-binap (**4**)	52	>98:2	
5	$Cu(CH_3CN)_4PF_6$	THF	KHMDS	(±)-binap (**4**)	62	>98:2	
6	$Cu(CH_3CN)_4PF_6$	THF	KO^{t}Bu	(±)-binap (**4**)	64	>98:2	
7	$Cu(CH_3CN)_4PF_6$	THF	KO^{t}Bu	(*R*)-binap (**4**)	38	>98:2	36
8	$Cu(CH_3CN)_4PF_6$	THF	KO^{t}Bu	(*R*)-Josiphos (**5**)	68	>98:2	48
9	$Cu(CH_3CN)_4PF_6$	THF	KO^{t}Bu	(*R*)-Fesulphos (**6**)	78	>98:2	68
10	$Cu(CH_3CN)_4PF_6$	toluene	KO^{t}Bu	(*R*)-Fesulphos (**6**)	78	>98:2	84
11[d]	$Cu(CH_3CN)_4PF_6$	toluene	KO^{t}Bu	(*R*)-Fesulphos (**6**)	59	>98:2	90
12[e]	$Cu(CH_3CN)_4PF_6$	toluene	KO^{t}Bu	(*R*)-Fesulphos (**6**)	93	>98:2	90
13[d,e,f]	$Cu(CH_3CN)_4PF_6$	toluene	KO^{t}Bu	(*R*)-Fesulphos (**6**)	84	>98:2	90
14[d,e,g]	$Cu(CH_3CN)_4PF_6$	toluene	KO^{t}Bu	(*R*)-Fesulphos (**6**)	66	>98:2	90

[a]Isolated yield. [b]Determined by ^{1}H NMR. [c]Determined by HPLC. [d]Reaction run at 0 °C. [e]2 equiv of **1a**. [f]5 mol % of catalyst. [g]3 mol % of catalyst.

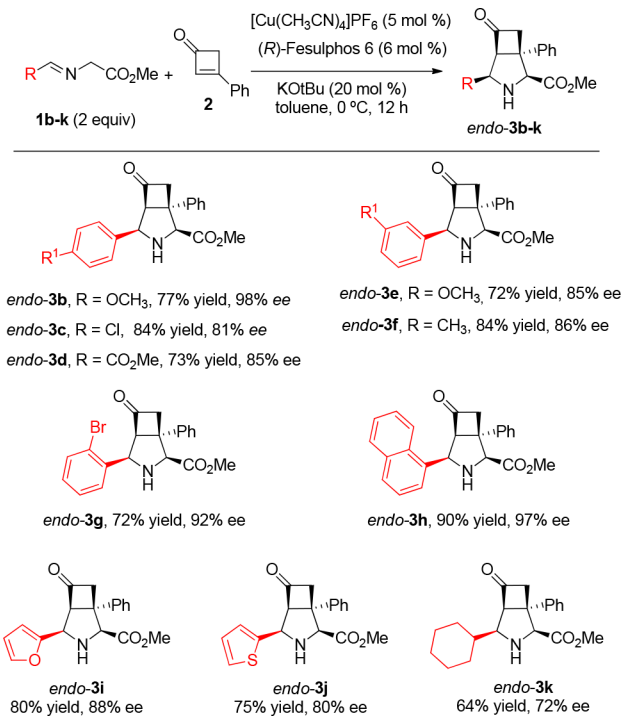
demanding substrates could participate in this reaction. Furthermore, the resulting cycloadducts could be interesting scaffolds for further transformations.

We chose iminoester **1a** and 3-phenylcyclobutenone **2a** as model substrates to optimize the reaction conditions. We began studying the effect of the metal source and the base in the presence of (±)-Binap as a ligand and THF as a solvent (see Table 1, entries 1–6). The use of Et_3N in combination with either silver or copper salts failed to promote the cycloaddition (Table 1, entries 1 and 2). Satisfyingly, a stronger base such a KO^{t}Bu or KHMDS provided the expected cycloadduct with moderate yield and almost complete endo selectivity (Table 1, entries 3–6). The combination of $Cu(CH_3CN)_4PF_6$ and KO^{t}Bu afforded the best result (Table 1, entry 6).

Once we demonstrated the viability of the reaction, a survey of chiral ligands were tested (Table 1, entries 7–14). A promising 36% ee was obtained with (*R*)-binap (Table 1, entry 7). After further screening of ferrocenyl ligands, we found that a Fesulphos ligand was the most efficient, furnishing the azabicycle *endo*-**3** in 78% yield and 68% ee (Table 1, entry 9). The enantioselectivity increased to 84% ee by performing the reaction in toluene (Table 1, entry 10) and lowering the temperature to 0 °C led to an additional improvement to 90% ee, albeit with a lower yield (59% yield; see Table 1, entry 11). Interestingly, an excellent yield was obtained using an excess of the iminoester (2 equiv, 93%; see Table 1, entry 12). A similar outcome was observed when the catalyst loading was reduced to 5 mol % (Table 1, entry 13), but additional reduction to 3 mol % led to a significant decrease in the reactivity (66% yield; see Table 1, entry 14).

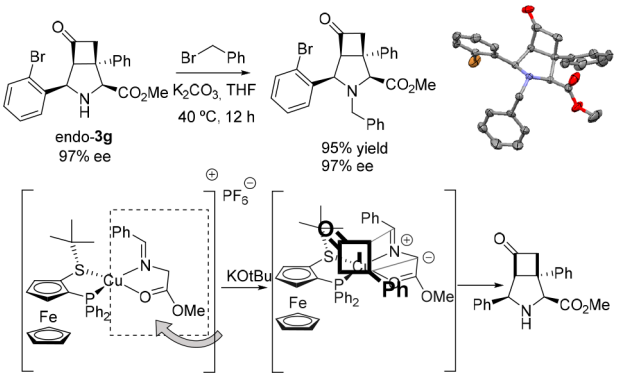
The substrate scope with regard to the iminoester was next evaluated (see Scheme 2). First, an array of iminoesters derived from aromatic aldehydes was examined. The [3 + 2] cycloaddition with either electron-donating or electron-withdrawing substituents at the *para* position of the aromatic ring afforded selectively the corresponding *endo*-azabicycles **3b**–**3d** with good yields (73%–84%) and asymmetric inductions ranging from 81% to 98% ee. Aromatic iminoesters with *meta* or *ortho* substituents provided a similar result (cycloadducts **3e**–**3g**), as well as the 1-naphthyl derivative (adduct **3h**).The cycloaddition was equally effective with heteroaromatic-substituted iminoesteres such as furyl **1i** and thienyl **1j**. Interestingly, the less-reactive cyclohexyl iminoester **1k** proved also to be a suitable substrate, leading to the pyrrolidine *endo*-**3k** with 64% yield and 72% ee.

Scheme 2. Scope with Regard to the Azomethine Ylide Precursor



The absolute and relative configuration of azabicycle *endo*-**3g** was unambiguously established by X-ray diffraction (XRD) of its corresponding benzyl derivative.[10] The observed enantioselectivity is in agreement with the model proposed to explain the origin of the high enantiocontrol attained by a Cu^{I}/(R)-Fesulphos complex in 1,3-dipolar cycloadditions.[11] Thus, the approach of the cyclobutenone would occur by the less-hindered face of the tetrahedral Fesulphos-iminoester copper complex, avoiding the steric interaction with the bulky ^{t}Bu group (see Scheme 3).

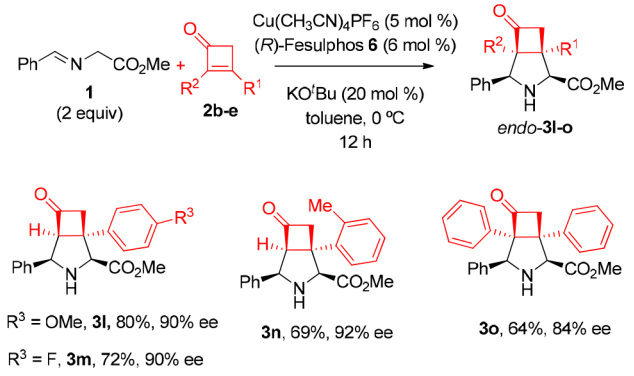
Scheme 3. X-ray Structure of *endo*-3g[a] and Proposed Stereochemical Model



[a]Hydrogen atoms have been removed for the sake of clarity.

The scope of the reaction regarding the substitution at the cyclobutenone partner is summarized in Scheme 4. Under the

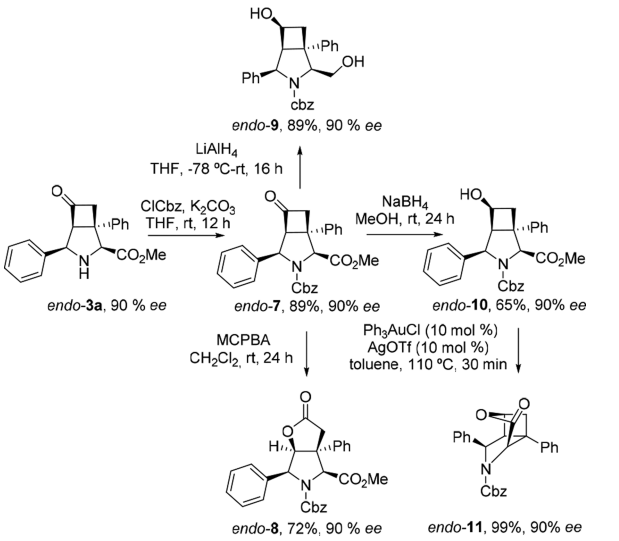
Scheme 4. Scope with Regard to the Cyclobutenone



previously optimized reaction conditions, all the [3 + 2] cycloadditions occurred with practically complete diastereoselectivity and high enantioselectivity, regardless of the *para* or *ortho* position of the substituent at the aromatic ring of the 3-arylcyclobutenone (adducts **3l**–**3n**). Outstandingly, the sterically very demanding 2,3-diphenyl cyclobutenone **2e** also reacted satisfactorily, affording the adduct **3o**, because of two adjacent all-carbon quaternary stereocenters, in 64% yield and 84% ee.

In order to highlight the versatility of the bicyclic adducts to the enantioselective synthesis of fused pyrrolidine derivatives, some transformations were conducted (see Scheme 5). Treatment of *endo*-**3a** (90% ee) with benzyl chloroformate in the presence of K_2CO_3 afforded the corresponding enantioenriched carbamate **7**, which was readily transformed to the

Scheme 5. Synthetic Transformations of *endo*-3a



corresponding bicyclic lactone **8** (72% yield) by Baeyer–Villiger oxidation, using the standard conditions. A reduction of carbamate **7** with $LiAlH_4$ provided selectively the diol **9**, while carbonyl reduction with $NaBH_4$, followed by treatment with a cationic gold complex, led to the tricyclic transesterification product **11**. Products **8**–**11** were isolated as single diastereomers with similar enantiopurity (90% ee)

In conclusion, a practical asymmetric [3 + 2] cycloaddition of azomethine ylides and cyclobutenones has been developed. In the presence of Cu^{I}/(*R*)-Fesulphos as a catalyst system, this reaction delivered valuable 3-azabicyclo[3.2.0]-heptanes with very high diastereoselectivity and excellent enantioselectivity. The synthetic potential of the cycloaddition was highlighted by the preparation of a variety of fused pyrrolidine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00936.

Experimental procedures, ^{1}H and ^{13}C NMR spectra for all new compounds, copies of HPLC chromatograms used to determine the enantiomeric purity (PDF)

Accession Codes

CCDC 1828413 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: javier.adrio@uam.es (J. Adrio).
*E-mail: juancarlos.carretero@uam.es (J. C. Carretero).

ORCID

Javier Adrio: 0000-0001-6238-6533

Author Contributions

[§]The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. These authors contributed equally.

Notes

The authors declare no competing financial interest.

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