Phosphoramidite-Cu(OTf)$_2$ Complexes as Chiral Catalysts for 1,3-Dipolar Cycloaddition of Iminoesters and Nitroalkenes

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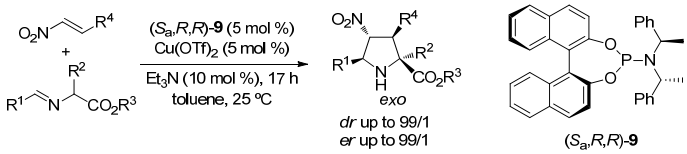
ABSTRACT



Chiral complexes formed by phosphoramidites such as (*S*$_a$,*R*,*R*)-9 and Cu(OTf)$_2$ are excellent catalysts for the general 1,3-dipolar cycloaddition between azomethine ylides and nitroalkenes affording the corresponding tetrasubstituted proline esters mainly as *exo*-cycloadducts in high *er* at room temperature. The *exo*-cycloadducts can be obtained in enantiomerically pure form just after simple recrystallization. DFT calculations support the stereochemical results.

Substituted prolinates **1**, obtained from the corresponding 1,3-dipolar cycloadditions (1,3-DC)[1] between glycine ester aldimines and nitroalkenes, are important inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis.[2] The most simple prolines *exo*-**2** have been recently used as chiral organocatalysts in aldol reactions.[3] In particular, for the asymmetric 1,3-DC of nitroalkenes as dipolarophiles chiral copper(I) complexes, formed from ferrocenyl-type phosphanes, have been mainly used as catalysts.[3,4] Copper(I) complexes **3**,[4a,c] **4**,[4b,e] and **5**,[3] generally afforded *exo*[5]-cycloadducts, whereas the corresponding *endo*-diastereomers have been prepared using complex **6**.[3] However, when copper(II) triflate and chiral ligand PyBidine[6] were combined the resulting catalyst **7** afforded

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(5) The *endo/exo* descriptor refers the approach of the electron-withdrawing group to the metallodipole before the cycloaddition.

(6) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338.

mainly *endo*-cycloadducts. In the case of 1,3-DC of glycinamides and nitrostyrene (*R*)-Segphos and $Cu(CH_3CN)_4PF_6$ as catalytic mixture, furnished *exo*-cycloadducts in good yields (up to 76%) and up to 96:4 *er*.[7] A 5-position epimer (called *exo*'-diastereoisomer) was mainly obtained when a solid-phase imidazolidine-aminophenol/$Ni(OAc)_2$ was employed.[8] Other chiral metal complexes such as $[BinapAuTFA]_2$ afforded modest results for the cycloaddition of methyl benzylideneaminoglycinate and nitrostyrene (up to 80:20 *dr* and 85:15 *er*).[9] On the other hand, benzophenone-derived *N*-(diphenylmethylene) glycinates have also been employed as azomethine ylide precursors in the presence of chiral silver catalysts,[10] and organocatalysts.[11] In general, only glycinate derived imino esters have been employed as azomethine ylide precursors except in the case of the ligand **7**-$Cu(OTf)_2$ which catalyzed the 1,3-DC with the corresponding alaninate. In many of these examples the elucidation of the reaction pathways has been studied by both DFT calculations[12] and experimentally.[4e]

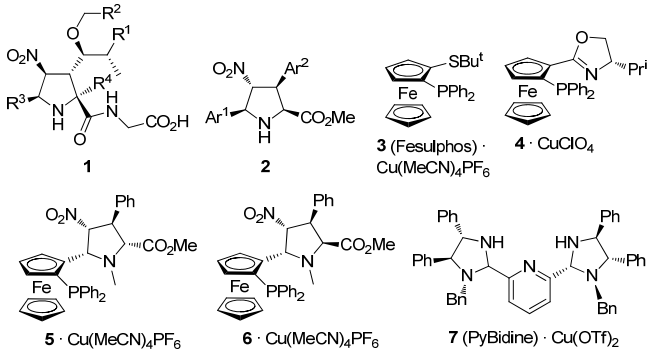

Figure 1. Useful nitro-substituted prolines **1** and **2**, and previously reported chiral catalysts for the enantioselective 1,3-DC of imino esters and nitroalkenes.

We envisaged that the use of chiral phosphoramidites **8** and **9**,[13] as monodentate privileged ligands,[14] could be a good alternative to the described sophisticated ligands for copper salts[15] to be used as chiral catalysts in the general asymmetric 1,3-DC of azomethine ylides, derived from α-amino acids, and nitroalkenes.

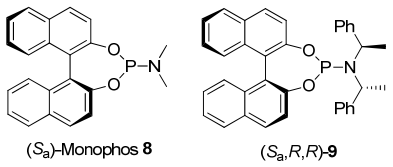

Figure 2. Employed chiral phosphoramidites

Initially, we selected (S_a)-Monophos **8** and (S_a,*R*,*R*)-**9** as chiral phosphoramidites for the preliminary catalyzed 1,3-DC between methyl *N*-benzylideneglycinate **10a** and β-nitrostyrene **11a**, in toluene as solvent, at room temperature for 17 h (25 ºC, Table 1). When (S_a)-Monophos **8**-$Cu(OTf)_2$ was used as catalyst mainly racemic *endo*-**2a** was obtained (Table 1, entry 1). However, in the case of (S_a,*R*,*R*)-**9**-$Cu(OTf)_2$, 88/11 *dr* and excellent enantioselection >99:1 was obtained for the *exo*-diastereoisomer **2a** (Table 1, entry 2). When using the enantiomeric ligand (R_a,*S*,*S*)-**9** the corresponding enantiomer *exo*-**2a** was mainly isolated (Table 1, entry 3). By contrast, complex formed by phosphoramidite (S_a,*S*,*S*)-**9** and $Cu(OTf)_2$ demonstrated to be a mismatched combination because the reaction gave the oposite diastereoselection with nule enantioselection (Table 1, entry 4). $Cu(OTf)_2$ was the most appropriate copper(II) salt rather than $Cu(OAc)_2$ in terms of both diastereo- and enantioselection (Table 1, compare entries 2 and 5). Copper(I) bromide did not afford the expected results, whilst $Cu(OTf)\cdot C_6H_6$ showed the same result that the obtained in the reaction run with $Cu(OTf)_2$ (Table 1, entries 6 and 7). We selected the catalyst formed by $Cu(OTf)_2$ because reactions involving copper(I) usually require inert atmosphere and degassed solvents in order to avoid dismutation. The presence of an external base is crucial for the reaction success, triethylamine being more adequate than DIPEA, and DABCO (Table 1, compare entry 2 with entries 8-10). The solvent effect was also dramatic because almost racemic mixtures of the product **2a** were isolated when Et_2O, THF, MeCN or DCM were employed, although in the last example the diastereomeric *exo/endo* ratio was the highest achieved in this transformation and in very good yields (Table 1, entries 11-14). Unexpectely, in all the cases, cycloadduct *endo*-**2a** was obtained in racemic form.

Smaller amounts of a catalyst loading (3 mol%) in the reaction gave lower yield (55%) and similar enantioselectivity of **2a** (not included in Table 1). The absolute configuration of *exo*-cycloadduct **2a** was established according to the retention times in HPLC using chiral columns and comparison with the data obtained for the same known product.[4c,9]

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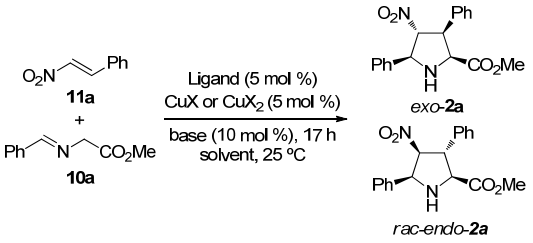
(12) For a review, see: de Cózar, A.; Cossío, F. P. *Phys. Chem. Chem.* **2011**, *13*, 10858.
(13) (a) Teichert, J. F.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2486. (b) *Privileged Chiral Ligands and Catalysts*; Qi-Lin Zhou, Ed.; Wiley-VCH: New York, 2011.
(14) The versatility and efficiency of chiral phosphoramidite **9**-$AgClO_4$ complex was described firstly by our group: (a) Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6055. (b) Nájera, C.; Retamosa, M. G.; Martín-Rodríguez, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2009**, 5622.
(15) Chiral phosphoramidite **9**-CuOTf has been isolated and characterized (IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, ^{19}F NMR, and HRMS) by Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. *Nature Chem.* **2012**, *4*, 649.

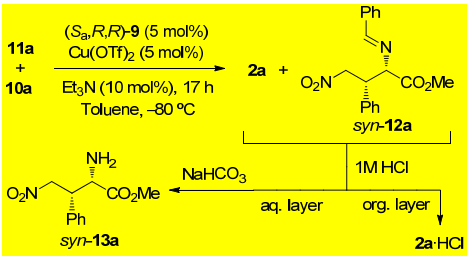
Table 1. Optimization of the 1,3-DC between **10a** and **11a**



	copper salt	solvent/ base	ligand	yield (%)[a]	*dr* [b]	er_{exo} [c]
1	$Cu(OTf)_2$	PhMe/Et_3N	(S_a)-**8**	78	24/76	50:50
2	$Cu(OTf)_2$	PhMe/Et_3N	(S_a,*R*,*R*)-**9**	79	89/11	>99:1
3	$Cu(OTf)_2$	PhMe/Et_3N	(R_a,*S*,*S*)-**9**	79	89/11	<1:99
4	$Cu(OTf)_2$	PhMe/Et_3N	(S_a,*S*,*S*)-**9**	16	20/80	50:50
5	$Cu(OAc)_2$	PhMe/Et_3N	(S_a,*R*,*R*)-**9**	41	68/32	94:6
6	CuBr	PhMe/Et_3N	(S_a,*R*,*R*)-**9**	nd	nd	nd
7	Cu(OTf)[d]	PhMe/Et_3N	(S_a,*R*,*R*)-**9**	78	89/11	>99:1
8	$Cu(OTf)_2$	PhMe/none	(S_a,*R*,*R*)-**9**	16	20/80	50:50
9	$Cu(OTf)_2$[e]	PhMe/DIPEA	(S_a,*R*,*R*)-**9**	13	66/34	70:30
10	$Cu(OTf)_2$[f]	PhMe/DABCO	(S_a,*R*,*R*)-**9**	79	84/16	50:50
11	$Cu(OTf)_2$[g]	Et_2O/Et_3N	(S_a,*R*,*R*)-**9**	50	78/22	58:42
12	$Cu(OTf)_2$[h]	THF/Et_3N	(S_a,*R*,*R*)-**9**	70	84/16	55:45
13	$Cu(OTf)_2$[i]	MeCN/Et_3N	(S_a,*R*,*R*)-**9**	40	64/36	55:45
14	$Cu(OTf)_2$[j]	DCM/Et_3N	(S_a,*R*,*R*)-**9**	82	93/4	50:50

[a] Isolated yield of the *exo*-cycloadduct after flash chromatography. [b] *exo/endo* ratio from the crude product, determined by ^{1}H NMR. Other stereoisomers were detected in low proportions. [c] For the major stereoisomer. [d] Benzene complex.

The reaction of nitrostyrene **11a** and imino ester **10a** was studied at lower temperatures. At –80 ºC a 1:1 mixture of the corresponding *exo*-cycloadduct-**2a** and the *syn*-imino ester **12a** was obtained. After acidic treatment at –80 ºC and simple extractive work-up, the corresponding *syn*-amino ester **13a** and as *exo*-**2a** hydrochloride were isolated (Scheme 1). Diastereomeric ratios of **13a** and enantiomeric ratios of both *exo/endo*-**2a** and *syn*-**13a** were independent of the working temperature.[16]



Scheme 1. Reaction at low temperature.

The scope of the reaction was surveyed by modifying the structure of the 1,3-dipole precursor and then varying the nitroalkene aromatic substituent (Table 2). The presence of an isopropyl group in the ester moiety improved the *exo/endo* ratio of the result obtained for the methyl ester derivative keeping the same enantioselection, but the reaction of the isopropyl ester afforded larger amounts of other steresoisomers (*ca.* 20%) (Table 2, entries 1 and 2). When α-substituted amino acids, such as leucine, and phenylalanine, were employed in the elaboration of imino esters **10** moderate yields of enantiomerically enriched *exo*-cycloadducts **2c**-**2d** were isolated (Table 2, entries 3, and 4). The stereochemical course or the reaction was also influenced by the aryl substituent of the imino ester (Table 2, entries 5-10). Thus, a methyl group bonded at the *o*-position decreased both, the diastereo- and enantiomeric ratios in **2e** (Table 2, entry 5). The *m*- and *p*-substitution increased these two parameters up to 89/11 *exo/endo* ratio with higher enantioselections 90:10 and 94:6 *er* for compounds **2f** and **2g**, respectively (Table 2, entries 6 and 7). Other *p*-halogen-substituted imino esters gave very good results, especially the fluoroaryl derivative **2i**, which was obtained with a 99:1 *er* (Table 2, entries 8 and 9). The 2-naphthyl derivative also gave a similar diastereoselection (86/14) although the *er* of product **2j** was sensibly lower (85:15) (Table 2, entry 10).

Several β-arylnitroalkenes were allowed to undergo this 1,3-DC employing imino ester **10a** (Table 2, entries 11-17). The *o*-substituted aryl group afforded very good enantioselection with lower *endo/exo* ratio in **2k** than the corresponding *m*- and *p*-substituted alkenes as, for example, **2l** and **2m** (Table 2, entries 11-13). Again, the *p*-substitution (Table 2, entries 13-17) resulted to be most favorable for this transformation such as it was exemplified by molecules **2o** and **2p** (Table 2, entries 15 and 16). Again, the presence of the isopropyl ester afforded the same results obtained when methyl ester was used (Table 2, compare entries 13 and 14). The same enantioselection was achieved with both esters but better diastereoselection was got using the methyl substituent. Heteroaryl substituents anchored to the imino ester did not afford any profitable result except the 2-furyl substituent in the dipolarophile skeleton generated product **2r** in moderate yield, and good diastereo- and enantiomeric ratio (Table 2, entry 18). The reaction performed with an aliphatic nitroalkene (R^4 = cyclohexyl) the corresponding *endo*-**2** derivative was obtained as a racemic mixure in moderate yield and impurified with other diastereoisomers (not included in Table 2).

Table 2 also shows chemical yields and enantiomeric ratios of recrystallized solid compounds previously purified by flash chromatography. In all these examples the diastereoselectivity was excellent affording exclusively the *exo*-derivative **2**. The enantiomeric ratio was notably increased after recrystallization of purified adducts **2** obtaning almost enantiopure samples (Table 2, entries 7-13, 15 and 16-17). An exception was the example performed with *o*-methyl substituted imino ester **10** whose *er* could not be improved (Table 2, entry 5).

In our hands, (S_a,*R*,*R*)-**9**-$Cu(OTf)_2$ complex could not be successfully recrystallized. However, ^{31}P NMR spectra revealed a signal at 57.14 ppm and a monomeric structure can be postulated as catalytic species according to electrospray ionization-MS (M^+, 602)[16] and the lack of non-linear effects (NLE).[14]

(16) See, supporting information for more details.

DFT calculations on the (S_a,*R*,*R*)-**9**·Cu(OTf)$_2$ catalyzed reaction to obtain **2a**, showed that the coordination sphere of Cu(II) atom is saturated by a OTf moiety. The most stable transition structures located are depicted in Figure 3. (*S*,*S*)-*exo*-**TS1-2a** was found to be about 1.5 kcal mol^{-1} more stable than its enantiomeric counterpart. These calculations support a computed er_{exo} of about 92%, in good agreement with the experimental results.

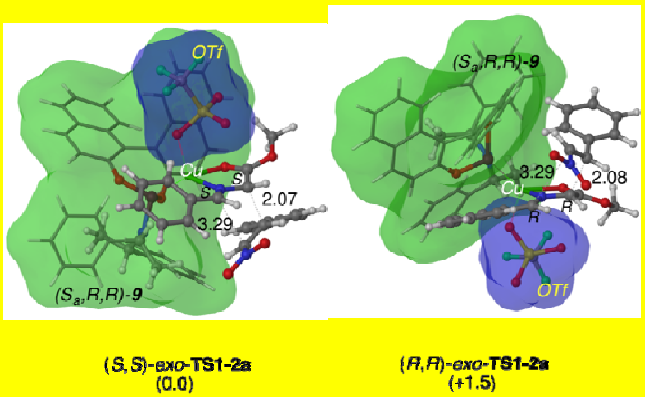


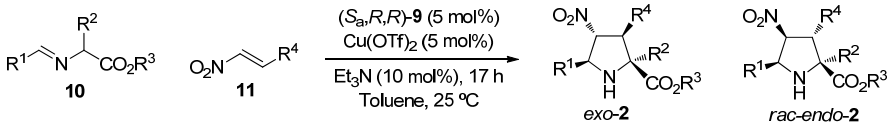
Figure 3. Main geometric features and relative energies (in kcal mol^{-1}) of the computed transition structures associated with the first step of the reaction between **11a** and (S_a,*R*,*R*)-**9**·CuOTf-**II** with **10a** computed at M06/LANL2DZ//ONIOM (B3LYP/LANL2DZ:UFF) + ΔZPCE level of theory. Bond-lengths are given in Å. The chiral ligand and OTf moiety are highligted in green and blue, respectively.

In summary, we can conclude that chiral phosphoramidites can be used as very good privileged ligands in the copper(II)-catalyzed 1,3-DC of azomethine ylides with β-nitrostyrenes at room temperature. In general, aromatic substituents in both components of the reaction are suitable. These simple reaction conditions allow the preparation of a variety of prolines **2**; useful candidates for organocatalyzed asymmetric aldol reactions.[3] A notable increment of the enantiomeric ratio occurred by recrystallization of the purified *exo*-products. The isolation of Michael-type addition compounds at lower temperatures supported the existence of a stepwise mechanism. The experimentally obtained diastereo- and enantioselectivities were supported by DFT calculations.

Acknowledgments. This work has been supported by the Spanish Ministerio de Economía y Competitividad (MINECO) (Consolider INGENIO 2010 CSD2007-00006, CTQ2010-20387), FEDER, Generalitat Valenciana (PROMETEO/2009/039), and by the University of Alicante. L. M. C. thanks the MINECO for a FPI fellowship. The DIPC and the SGI/IZO-SGIker UPV/EHU (European Social Fund) are gratefully acknowledged for generous allocation of computational resources.

Supporting Information Available. Experimental procedures, full spectroscopic data for all new compounds an computadional data are available free of charge via the Internet at http://pubs.acs.org.

Table 2. Scope of the 1,3-DC between iminoesters and nitroalkenes catalyzed by (S_a,*R*,*R*)-**9**·Cu(OTf)$_2$ complex.



entry	R^1	R^2	R^3	R^4	**2**	yield (%)[a]	*exo/endo*[b]	er_{exo}	yield (%)[c]	er_{exo}[d]
1	Ph	H	Me	Ph	**2a**	79	89/11	>99:1	68	>99:1
2	Ph	H	Pr^i	Ph	**2b**	69[e]	99/1	>99:1	60	>99:1
3	Ph	H	Bu^i	Ph	**2c**	60	92/8	>99:1	47	>99:1
4	Ph	H	$PhCH_2$	Me	Ph	**2d**	65	75/25	>99:1	51
5	2-MeC_6H_4	H	Me	Ph	**2e**	51	59/41	75:25	37	77:23
6	3-MeC_6H_4	H	Me	Ph	**2f**	61	79/21	90:10	-[f]	-[f]
7	4-MeC_6H_4	H	Me	Ph	**2g**	59	79/21	94:6	46	99:1
8	4-BrC_6H_4	H	Me	Ph	**2h**	76	89/11	95:5	69	99:1
9	4-FC_6H_4	H	Me	Ph	**2i**	70	87/13	99:1	62	>99:1
10	2-Naphthyl	H	Me	Ph	**2j**	70	86/14	85:15	59	94:6
11	Ph	H	Me	2-BrC_6H_4	**2k**	56	73/27	96:4	48	98:2
12	Ph	H	Me	3-BrC_6H_4	**2l**	61	90/10	94:6	52	98:2
13	Ph	H	Me	4-BrC_6H_4	**2m**	70	86/14	95:5	64	99:1
14	Ph	H	Pr^i	4-BrC_6H_4	**2n**	72	80/20	95:5	-[f]	-[f]
15	Ph	H	Me	4-MeC_6H_4	**2o**	48	82/18	99:1	40	99:1
16	Ph	H	Me	4-(MeO)C_6H_4	**2p**	68	72/28	98:2	63	99:1
17	Ph	H	Me	4-FC_6H_4	**2q**	73	82/12	96:4	70	99:1
18	Ph	H	Me	2-Furyl	**2r**	41	77/23	91:9	-[f]	-[f]

[a] Isolated yield of the major cycloadduct after flash chromatography (SiO_2). [b] From the crude product, determined by ^{1}H NMR. Other stereoisomers were detected in low proportions. [c] Isolated yield after recrystallization for the *exo*-adduct based on the starting compound **10**. [d] After recrystallization. [e] 20% of the other stereoisomers were also obtained. [f] Oily products.