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

Luis M. Castelló,[†] Carmen Nájera,[†] José M. Sansano,*[,†]
Olatz Larrañaga,[‡] Abel de Cózar,[‡,§] and Fernando P. Cossío[‡]

Departamento de Química Orgánica e Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Universidad de Alicante, 03080-Alicante, Spain, Departmento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, P. K. 1072, E-20018 San Sebastián, Spain, and IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

jmsansano@ua.es

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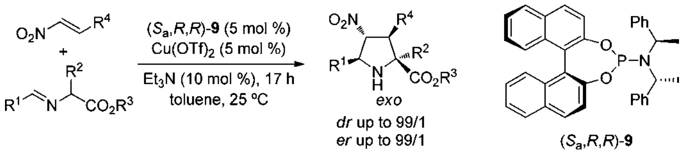
ABSTRACT



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** (Figure 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 mainly *endo*-cycloadducts. In the case of 1,3-DC of glycinamides and nitrostyrene (R)-Segphos and Cu(CH$_3$CN)$_4$PF$_6$ as a catalytic mixture, *exo*-cycloadducts were furnished 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

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[†] Universidad de Alicante.
[‡] Universidad del País Vasco.
[§] Basque Foundation for Science.

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complexes such as $[BinapAuTFA]_2$ afforded modest results for the cycloaddition of methyl benzylideneglycinate 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** and $Cu(OTf)_2$ 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 experimental results.[4e]

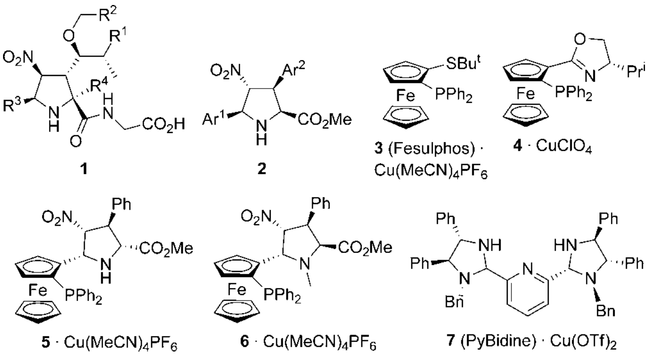

Figure 1. Useful nitro-substituted prolines **1** and **2** and previously reported chiral catalysts for the enantioselective 1,3-DC of imino esters and nitroalkenes.

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.

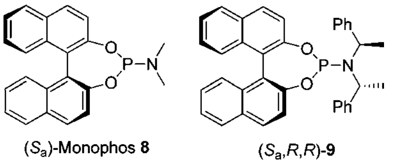

Figure 2. Employed chiral phosphoramidites.

Initially, we selected (S_a)-Monophos **8** and (S_a,*R*,*R*)-**9** (Figure 2) as chiral phosphoramidites for the preliminary catalyzed 1,3-DC between methyl *N*-benzylideneglycinate **10a** and *β*-nitrostyrene **11a**, in toluene as solvent, at rt for 17 h (25 °C, Table 1). When (S_a)-Monophos **8**·$Cu(OTf)_2$ was used as the 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 were 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, the complex formed by phosphoramidite (S_a,*S*,*S*)-**9** and $Cu(OTf)_2$ demonstrated to be a mismatched combination because the reaction gave the opposite diastereoselection with no 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, while $Cu(OTf){\cdot}C_6H_6$ showed the same result that was 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 an 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, MeCN, or DCM was 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). Unexpectedly, in all the cases, cycloadduct *endo*-**2a** was obtained in racemic form.

Smaller amounts of a catalyst loading (3 mol %) in the reaction gave a lower yield (55%) and an enantioselectivity similar of that 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]

The reaction of nitrostyrene **11a** and imino ester **10a** was studied at lower temperatures. At −80 °C a 1:1 mixture of the corresponding *exo*-cycloadduct-**2a** and the *syn*-imino ester **12a** was obtained. After acidic treatment at −80 °C and simple extractive workup, the corresponding *syn*-amino ester **13a** and *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]

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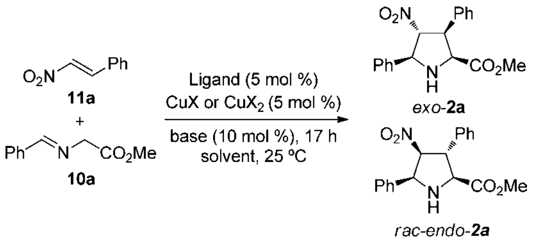
[15] Chiral phosphoramidite **9**−CuOTf has been isolated and characterized (IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, ^{19}F NMR, and HRMS) by: Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. *Nat. Chem.* **2012**, *4*, 649.

[16] See Supporting Information for more details.

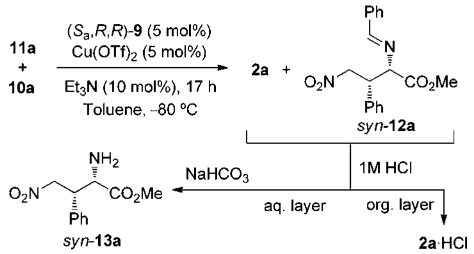
Table 1. Optimization of the 1,3-DC between **10a** and **11a**



	Cu 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	$Cu(OTf)_2$	PhMe/DIPEA	(S_a,R,R)-**9**	13	66/34	70:30
10	$Cu(OTf)_2$	PhMe/DABCO	(S_a,R,R)-**9**	79	84/16	50:50
11	$Cu(OTf)_2$	Et_2O/Et_3N	(S_a,R,R)-**9**	50	78/22	58:42
12	$Cu(OTf)_2$	THF/Et_3N	(S_a,R,R)-**9**	70	84/16	55:45
13	$Cu(OTf)_2$	MeCN/Et_3N	(S_a,R,R)-**9**	40	64/36	55:45
14	$Cu(OTf)_2$	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.

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** and **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 an *exo*/*endo* ratio of 89/11 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).

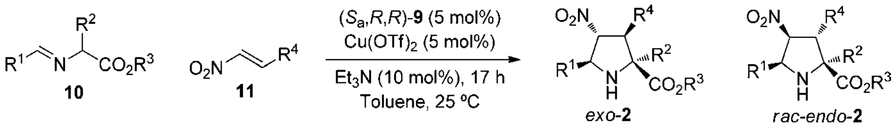
Several β-arylnitroalkenes were allowed to undergo this 1,3-DC employing imino ester **10a** (Table 2, entries 11−17). The *o*-substituted aryl group afforded very good enantioselection with a lower *endo*/*exo* ratio in **2k** than the corresponding *m*- and *p*-substituted alkenes as, for example, **2l** and **2m** (Table 2, entries 11−13). Again, the *p*-substitution (Table 2, entries 13−17) resulted in being the most favorable for this transformation, 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 obtained 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) afforded the corresponding *endo*-**2** derivative 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** obtaining almost enantiopure samples (Table 2, entries 7−13 and 15−17). 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, the (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 the catalytic species according to electrospray ionization-MS (M^+, 602)[16] and the lack of nonlinear effects (NLE).[14]

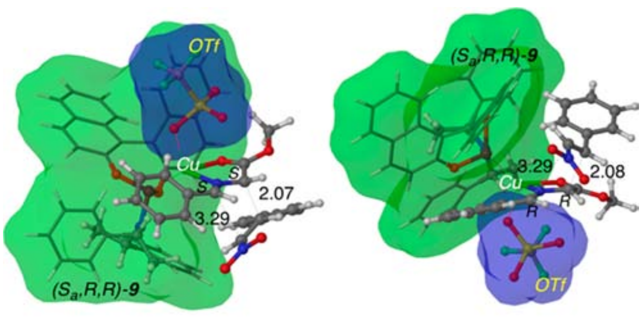
DFT calculations on the (S_a,R,R)-**9**·$Cu(OTf)_2$ catalyzed reaction to obtain **2a** showed that the coordination sphere of the Cu(II) atom is saturated by an OTf moiety. The most stable transition structures located are depicted in Figure 3. (S,S)-*exo*-**TS1**−**2a** was found to be about 1.5 kcal 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.

Table 2. Scope of the 1,3-DC between Iminoesters and Nitroalkenes Catalyzed by the (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	Bu^i	Me	Ph	**2c**	60	92/8	>99:1	47	>99:1
4	Ph	PhCH_2	Me	Ph	**2d**	65	75/25	>99:1	51	>99:1
5	$2\text{-MeC}_6\text{H}_4$	H	Me	Ph	**2e**	51	59/41	75:25	37	77:23
6	$3\text{-MeC}_6\text{H}_4$	H	Me	Ph	**2f**	61	79/21	90:10	–[f]	–[f]
7	$4\text{-MeC}_6\text{H}_4$	H	Me	Ph	**2g**	59	79/21	94:6	46	99:1
8	$4\text{-BrC}_6\text{H}_4$	H	Me	Ph	**2h**	76	89/11	95:5	69	99:1
9	$4\text{-FC}_6\text{H}_4$	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	$2\text{-BrC}_6\text{H}_4$	**2k**	56	73/27	96:4	48	98:2
12	Ph	H	Me	$3\text{-BrC}_6\text{H}_4$	**2l**	61	90/10	94:6	52	98:2
13	Ph	H	Me	$4\text{-BrC}_6\text{H}_4$	**2m**	70	86/14	95:5	64	99:1
14	Ph	H	Pr^i	$4\text{-BrC}_6\text{H}_4$	**2n**	72	80/20	95:5	–[f]	–[f]
15	Ph	H	Me	$4\text{-MeC}_6\text{H}_4$	**2o**	48	82/18	99:1	40	99:1
16	Ph	H	Me	$4\text{-(MeO)C}_6\text{H}_4$	**2p**	68	72/28	98:2	63	99:1
17	Ph	H	Me	$4\text{-FC}_6\text{H}_4$	**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.



(S,S)-*exo*-**TS1-2a**
(0.0)

(R,R)-*exo*-**TS1-2a**
(+1.5)

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 the 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 rt. 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.

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Supporting Information Available. Experimental procedures, full spectroscopic data for all new compounds, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.