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Efficient Diastereo- and Enantioselective Synthesis of *exo*-Nitroprolinates by 1,3-Dipolar Cycloadditions Catalyzed by Chiral Phosphoramidite·Silver(I) Complexes

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Dedicated to Prof. Max Malacria on the occasion of his 65th birthday

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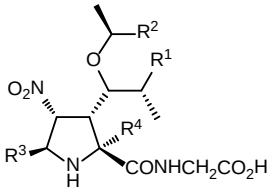
Abstract. Chiral complexes formed by privileged phosphoramidites and silver triflate or silver benzoate are excellent catalysts for the general 1,3-dipolar cycloaddition between azomethine ylides generated from α-amino acids derived imino esters and nitroalkenes affording with high *dr* the *exo*-cycloadducts 4,5-*trans*-2,5-*cis*-4-nitroprolinates in high *ee* at room temperature. In general, better results are obtained using silver than copper(II) complexes. In many cases the *exo*-cycloadducts can be obtained in enantiomerically pure form just after simple recrystallization. The mechanism and the justification of the experimentally observed stereodiscrimination of the process are supported by DFT calculations. These enantiomerically enriched *exo*-nitroprolinates can be used as reagents for the synthesis of nitropiperidines, by ester reduction and ring expansion, which are inhibitors of farnesyltransferase.

Keywords: Asymmetric synthesis; dipolar cycloaddition; azomethine ylides; phosphoramidite; silver

Introduction

Since the first catalytic enantioselective 1,3-dipolar cycloaddition (1,3-DC)[1] involving azomethine ylides and electrophilic alkenes was described in 2002 using chiral bisphosphine·silver(I)[2] and zinc(II)[3] complexes, a wide variety of silver and copper complexes have been mainly used for the diastereoselective synthesis of *endo* and *exo*-prolinates, respectively. The diastereo- and enantioselective generation of up to four stereogenic centers in only one step enhanced the interest of many researches also using chiral organocatalysts, allowing the synthesis of polysubstituted pyrrolidines (including prolines) with many interesting biological activities.[4]

As 1,3-dipole precursors *N*-arylidene-α-amino esters are generally used and electron-deficient alkenes are the most suitable dipolarophiles. Special mention has been paid to nitroalkenes,[1h] which introduces the versatile nitro group at the 4-position of the pyrrolidine skeleton. Particularly, *exo*-4-nitroprolinates with a 2,5-*cis*-4,5-*trans*-configuration **1** have been used as leukocyte function associated antigen-1 antagonists during a cancer evolution,[5] with important activity as inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis and even for treatments of other diseases.[6] More simple *exo*-nitroprolinates **2** have shown a high efficiency as organocatalysts in asymmetric aldol reactions.[7]



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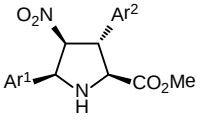

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Figure 1. Useful *exo*-nitroprolinates.

N-Arylideneamino esters **3** (Figure 2) have been employed as azomethine ylide precursors in the enantioselective 1,3-DC with nitroalkenes employing organocatalysts and chiral metal complexes. In the first example, a chiral thiourea **5**[8] catalyzed the 1,3-DC of a malonate derivative (**3**, $R^1 = CO_2Et$).[9] The major contributions using α-amino esters derived imines were achieved under the control of chiral Lewis acids[10] formed by copper(I) **6-9**,[11] copper(II) **10**,[12a] and **11**[12b] gold(I) **12**[13] and nickel(II) **13**[14] complexes. These metal complexes showed preferential *exo*-approaches[15] at their most favorable TS.

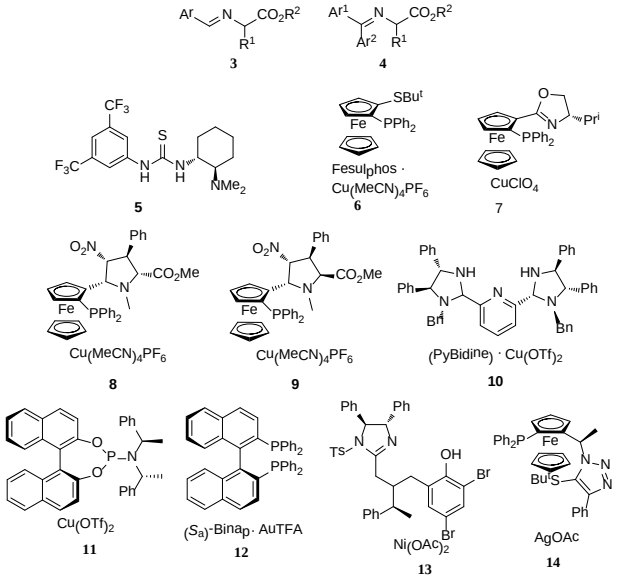


Figure 2. Iminoesters **3** and **4**, as precursors of stabilized azomethine ylides, and catalysts used for enantioselective 1,3-DC.

The only exception reported in all these reported examples is the employment of copper(II)·pyridyl bis(imidazolidine) **10** as chiral complex,[12a] which afforded the *endo*-adducts. A very interesting switchable system is catalyst of the type **7** by varying the electronic properties of the aryl groups of the P atom of the chiral P,N-ferrocene ligands.[11b]

With all these precedents, and taking in account that silver(I) is traditionally the most suitable cation to stabilize a metallodipole derived from iminoesters **3**,[16] it was curious not to find any efficient 1,3-DC with β–nitroalkenes.[17] Only Fukuzawa's group reported a highly effective asymmetric cycloaddition using glycine derived imino esters **4** (R^1 = H) and nitroalkenes catalyzed by silver(I)·thioclickferrophos complexes **14**.[18]

In this article, we will report the first highly efficient silver(I) catalyzed enantio- and diastereoselective 1,3-DC of iminoesters **3** and nitroalkenes testing privileged ligands such as (S_a)-Binap (**15**), (S_a)-Monophos (**16**), and phophoramidite **17** (Figure 3).

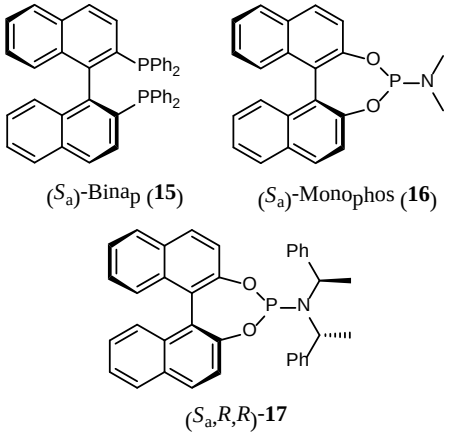


Figure 3. Chiral privileged ligands.

Results and Discussion

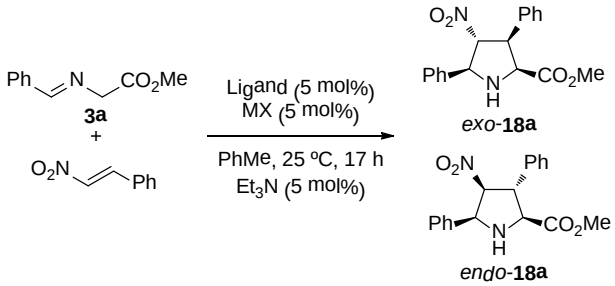
Initial studies for the cycloaddition of methyl benzylidenglycinate (**3a**) and nitrostyrene with Binap (**15**) and $AgClO_4$[19] or Monophos (**16**) and $AgClO_4$ as catalysts gave low conversions (Table 1, entries 1 and 2). In the second case equimolar mixture of *endo/exo* adducts were obtained with very low *ee* for the resulting *exo*-compound **18a** (Table 1, entry 2).[20] To our surprise, when the chiral complex formed between (S_a,*R*,*R*)-**17** and $AgClO_4$[21], related to the $Cu(OTf)_2$ complex **11**,[12b] product *exo*-**18a** was obtained with a 91/9 *dr* and 94% *ee* (Table 1, entry 3). Other different silver salts were then evaluated in the *in situ* generation of the corresponding **17**·silver(I) complex (5 mol% as optimal catalyst loading, 30 min, toluene at 25 ºC). The difference between using silver acetate and silver trifluoroacetate (TFA) was very significant in terms of both diastereo- and enantioselections (Table 1, compare entries 4 and 5). The highest enantiodiscrimination (98% *ee*) was achieved by the complex formed by phosphoramidite **17** or its enantiomer and silver benzoate (Table 1, entries 6 and 7). In addition, the reaction performed with silver triflate gave a lower *dr* than the analogous reaction catalyzed with silver perchlorate, but with slightly higher *ee* (Table 1, entry 8) served us to compare this work with the already published involving copper(II) triflate.[12b] A 99% *ee* of *exo*-**18a** with a slightly lower *dr* (89/11) was obtained in this last example (Table 1, entry 9).[12b]

Several solvents such as DCM, Et_2O, THF, and MeOH, as well as other different bases like DIPEA, DABCO, DBU did not improve the results obtained employing toluene as solvent and triethylamine (5 mol%) as base.

The absolute configuration of *exo*-cycloadduct **17a** was established according to the retention times

in HPLC using chiral columns and comparison with the data obtained for the same known product. [12b]

Table 1. Optimization of the 1,3-DC between imino ester **3a** and β-nitrostyrene.



Entry	Ligand	MX	Conv. [%] [a]	*exo*-/ *endo*-**18**[b]	*ee* [%][c]
1	**15**	$AgClO_4$	5	nd	nd
2	**16**	$AgClO_4$	45	54/46[d]	10
3	**17**	$AgClO_4$	>95	91/9	94
4	**17**	AgOAc	>95	90/10[d]	94
5	**17**	AgOTFA	>95	70/30[d]	89
6	**17**	AgOBz	>95	91/9	98
7	*ent*-**17**	AgOBz	>95	91/9	-96
8	**17**	AgOTf	>95	90/10[d]	96
9[e]	**17**	$Cu(OTf)_2$	95	89/11	99

[a] Unless otherwise specified: ligand (5 mol%), MX (5 mol%), **3a** (0.2 mmol), β-nitrostyrene (0.2 mmol), Et_3N (5 mol%) in toluene (2 mL), rt for 17 h.
[b] From the crude product, determined by ^1H NMR.
[c] For the major *exo*-stereoisomer.
[d] Other stereoisomers were detected in low proportions.
[e] Reference 12b
(nd = not determined).

In order to gain a better understanding of these experimental results and, in particular, the origins of the unexpected *exo*-selectivity found on the silver catalyzed 1,3-DC described on Table 1, DFT calculations were performed. We selected the reaction of imino ester **3a** and β-nitrostyrene in the presence of (S_a,*R*,*R*)-**17**·AgOTf catalytic system as a model reaction. In previously reported computational works we showed the importance of the counterion on the observed selectivity of the reaction.[12b, 22] Therefore, we included the OTf fragment in these calculations. The most stable *N*-metallated complexes computed at the ONIOM level of theory are depicted in Figure 4. Analogous previously reported copper(II) triflate complexes **11** are also included for comparison.[12 b]

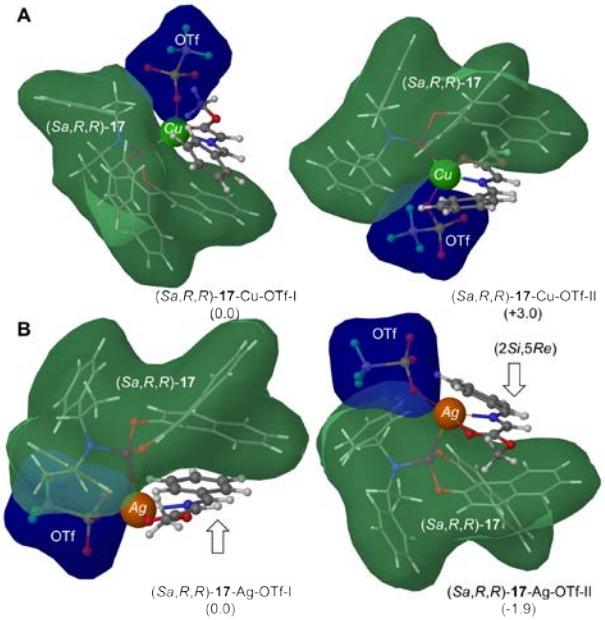


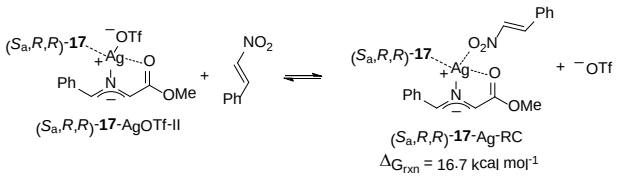
Figure 4. Structures and relative energies (in kcal mol^{-1}) of complexes derived from imine **3a** and (A) (S_a,*R*,*R*)-**17**·$Cu(OTf)_2$ and (B) (S_a,*R*,*R*)-**17**·AgOTf at M06/LANL2DZ//ONIOM(B3LYP/LANL2DZ:UFF)+Δ ZPCE level of theory. High and low-level atoms in ONIOM partitions are shown as ball & stick or tube representations, respectively. Green and blue surfaces represent solvent accessible surface areas of the chiral ligand and the triflate counterion, respectively. The hollow arrows show the preferential prochiral side of silver complexes.

These calculations show that the metallic centers are coordinated to both the nitrogen atom and the carboxy group of the azomethine ylide, to the phosphorous atom of chiral ligand **17** and to an oxygen atom of the triflate anion. Nevertheless, in both cases the coordination pattern is slightly different. Copper atom presents an almost regular tetrahedral environment in which both prochiral faces are partially blocked by the ligand or the triflate moiety. Calculations of the complete profile for copper complex showed that the blockage by triflate is more effective due to a Coulombic repulsion generated when the incoming dipolarophile approaches to the azomethine ylide complex.[12b] On the other hand, silver complexes present a trigonal pyramidal geometry in which the azomethine ylide, the silver atom and the oxygen of the OTf moiety are almost coplanar. In this case, only one of the prochiral faces is accessible, namely 2*Si*,5*Re*-face in the most stable ylide [(S_a,*R*,*R*)-**17**·Ag-OTf-II].

These computational results are compatible with ^{19}F-NMR experiments on $Cu(OTf)_2$ and AgOTf complexes of (S_a,*R*,*R*)-**17** and imine **3a** in

the absence of base. In the case of $Cu(OTf)_2$, the ^{19}F signals appears at δ -78.04 ppm, whereas when AgOTf the CF_3 resonance is observed at δ -78.58 ppm. These results indicate that in the former case the triflate anion is closer to the copper(II) centre, whereas in the latter case the average distance between Ag(I) and the triflate is longer, thus leaving one prochiral face less congested.[23]

In order to assess whether the OTf moiety remains close to the silver atom along the reaction coordinate, we computed the hypothetical OTf-β-nitrostyrene exchange on the metal coordination sphere to yield (*S*$_a$,*R*,*R*)-**17**·Ag-RC (Scheme 1). These results show that this process is endergonic, and no OTf-β-nitrostyrene exchange occurs during the reaction. Therefore, no stabilizing *endo* interaction between the silver and the nitro group can be expected along the reaction path.



Scheme 1. Reaction energy of the OTf-β-nitrostyrene exchange on the silver coordination sphere computed at M06/LANL2DZ//ONIOM(B3LYP/LANL2DZ:UFF) + ΔZPCE level of theory.

We also located the transition structures corresponding to the first step of the selected 1,3-DC reaction. The main geometric features and relative energies of the least energetic transition structures are collected in Figure 5.

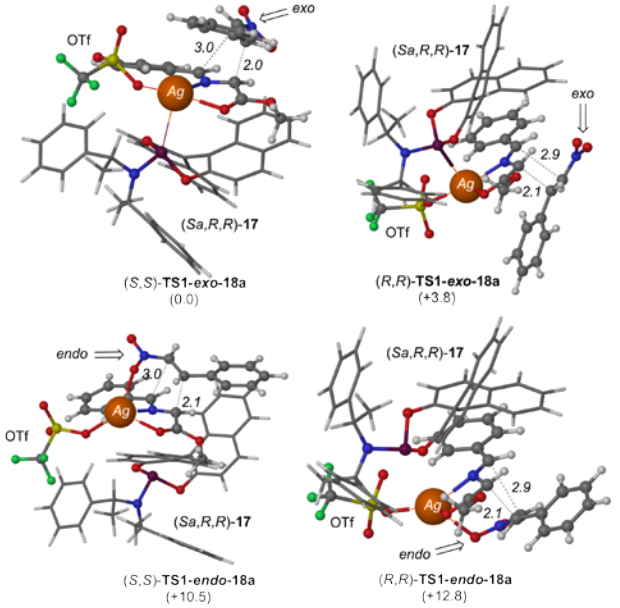


Figure 5. Main geometrical features and relative energies (in kcal mol^{-1}) of transition structures associated with the first step of the 1,3-DC reaction of imine **3a** and β-nitrostyrene catalyzed by (*S*$_a$,*R*,*R*)-**17**·AgOTf. See caption of Figure 4 for additional details. Distances are in Å.

The computed transition structures correspond to a stepwise mechanism[24] in which the first step consists in a Michael addition of the enolate moiety in the *N*-metallated azomethine ylide to β-nitrostyrene forming a zwiterionic intermediate (*S*,*S*)-**INT1** that undergoes an intramolecular Mannich-like reaction to yield the final cycloadduct (*vide infra*). Our results show the predicted preference of the *exo*-approaches over the *endo*-ones due to the presence of OTf on the silver coordination sphere. It is noticeable that in the *endo*-approaches, there are a lengthening of the P-Ag distance of about 1 Å compared to their *exo*-analogous. Moreover, the effective blockage of one prochiral face by the (*S*$_a$,*R*,*R*)-**17**·AgOTf catalytic system is pointed out by the energetic difference of 3.8 kcal mol^{-1} between (*S*,*S*)-**TS1-*exo*-18a** and (*R*,*R*)-**TS1-*exo*-18a** in favor to the former one. This energetic difference means a theoretical ee_{exo} of about 99%, in good agreement with the experimental results.

The complete reaction mechanism that yields the product *exo*-**18a** was also studied. The energetic profile and the main geometrical features of the second transition structure (*S*,*S*)-**TS2-*exo*-18** are depicted in Figure 6.

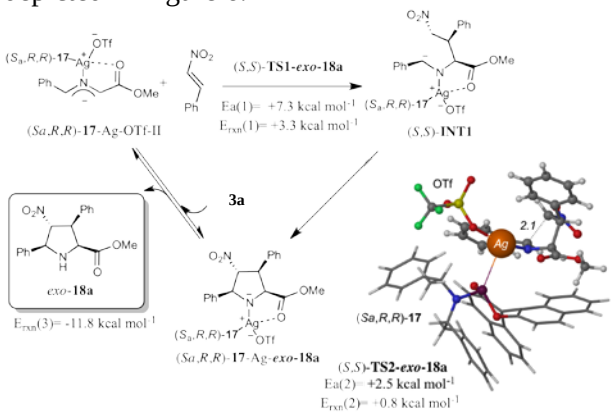


Figure 6. Main geometrical features of the second transition structure and relative energies (in kcal mol^{-1}) associated with the 1,3-DC reaction of imine **3a** and β-nitrostyrene catalyzed by (*S*$_a$,*R*,*R*)-**17**·AgOTf. See caption of Figure 4 for additional details. Distances are in Å.

The computed activation barrier associated with the second step was lower than the one associated to

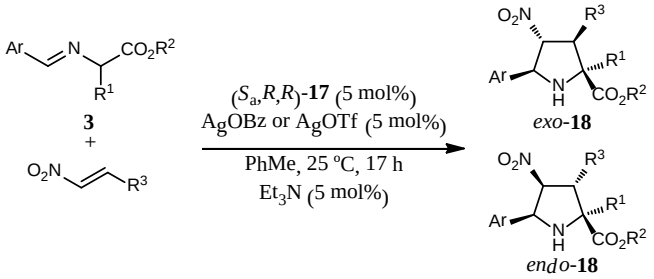
the first step *c.a*. 5 kcal mol^{-1}. It is noteworthy than the formation of the major complexed cycloadduct is thermodynamically disfavored. The driving force that ensures the completion of the catalytic cycle is the final equilibrium between the complexed and released (3+2) cycloadducts e*xo*-**18a**, that is highly exothermic [E_{rxn} (3) = 11.8 kcal mol^{-1}] thus ensuring the recovery of the reactive ylide complex.

The scope of the reaction was made with different nitroalkenes, α–amino esters and benzyliden imino esters (Scheme 2 and Table 2). Parallel studies were carried out for the reaction performed with ligand **17** and AgOTf or AgOBz. Firstly, the influence of an isopropyl instead of a methyl ester showed almost identical *ee* for the two silver complexes with a slightly better *exo*-diastereoselection for the isopropyl ester. However, the lower yield of the *exo*/*endo* mixture obtained in the case of the reaction with isopropyl ester obeyed to the appearance of a proportion of other unidentified diastereoisomers (*ca.* 28% from crude product determined by ^{1}H NMR), (Table 2, entries 1 and 2). In consequence, the study of the scope of the reaction was done with methyl esters as precursors.

The variation of the aryl substituent of the dipolarophile induced higher chemical yields, *exo*-diastereoselectivties and enantioselections in products **18** when the reactions occurred in the presence of (S_a,*R*,*R*)-**17**·AgOBz rather than with the triflate derivative (Table 2, entries 3-7). In particular, the heteroaromatic moiety bonded to the nitro component (2-furyl) was more appropriate for the system built with the chiral silver benzoate complex achieving 77% of chemical yield and 98% *ee* of *exo*-**18h** (Table 2, entry 8). In general, better results were observed with (S_a,*R*,*R*)-**17**·AgOBz than with $Cu(OTf)_2$.[12b] When the nitroalkene incorporated an aliphatic cyclohexyl group a reversal diastereoselectivity was observed in the **17**·AgOTf catalyzed 1,3-DC. The exclusive *endo* isomer was isolated in 71% yield but as a racemic mixture. However, an equimolar mixture of *endo/exo* diastereoisomers in 75% overall yield in the analogous reaction performed with AgOBz. Again, the adduct *endo*-**18i** was isolated as a racemate, whilst the *exo*-isomer **18i** was obtained in low 32% yield but with a 96% *ee* (Table 2, entry 9). On the other hand the 1,3-DC with this nitroalkene failed with the $Cu(OTf)_2$ complex **11**.[12b]

When alanine, leucine, and phenylalanine derived imino esters were employed as azomethine ylide precursors, an increment of the *endo*-diastereoisomer was observed. Chemical yields were moderate to good, maintaining a very high enantioselection for the *exo*-adducts **18j-l** (up to 99% *ee*). Higher amounts of other different diastereoisomers were identified in the crude reaction ^{1}H NMR spectra when these α-substituted iminoesters were used (Table 2, entries 10-12). However, in the case of the $Cu(OTf)_2$ complex **11,** the alanine derivative failed and in the case of leucine similar results were obtained than with AgOTf. On the other hand, for the phenylalanine imino ester the $Cu(OTf)_2$ catalyst **11** was better than the silver salts ones giving **18l** in 51% yield and 98% *ee*.[12b]

With respect to the use of different methyl benzylideneimino glycinates The more sterically hindered *o*-tolyl imino group also favoured the generation of the *endo*-isomer **18m** but in less proportion in the case of AgOBz than with $Cu(OTf)_2$. On the other hand, the *exo*-**18m** was obtained in a ee up to 90% with AgOBz towards 54% ee with $Cu(OTf)_2$ (Table 2, entry 13). It seems that the lower steric repulsion the higher proportion of *exo*-adduct and enantioselections. This effect can be observed in the series of *o*-, *m*-, and *p*-tolyl substituents (Table 2, entries 13-15). Other 4-substituted arenes also provided high diasteresoselections, good chemical yields and excellent enantioselections of compounds **18p-r** (Table 2, entries 16-18) under the presence of both of the chiral silver(I) complexes and with better results than with $Cu(OTf)_2$. Finally in the case of the 2-naphthyl substituent, *exo*-**18s** was obtained with up to 72% *de* and 85% *ee* when AgOTf was used better than $Cu(OTf)_2$ and AgOBz (Table 2, entry 19).



Scheme 2. Scope of the diastereo- and enantioselective 1,3-DC between imino esters **3** and nitroalkenes catalyzed by (S_a,*R*,*R*)-**17**·AgOBz or (S_a,*R*,*R*)-**17**·AgOTf.

Table 2. Scope of the diastereo- and enantioselective 1,3-DC between imino esters **1** and nitroalkenes catalyzed by (S_a,*R*,*R*)-**17**·AgOBz or (S_a,*R*,*R*)-**17**·AgOTf.[*]

						(S_a,*R*,*R*)-**17**·AgOTf			(S_a,*R*,*R*)-**17**·AgOBz		
Entry	Ar	R^1	R^2	R^3	**18**	*exo*/*endo*[a]	Yield [%][b]	*ee* [%][c]	*exo*/*endo*[a]	(%)[b] Yield	(%) *ee*[c]

1	Ph	H	Me	Ph	**18a**	90/10[d]	80 (65)	96 (99)	91/9	88	99
2	Ph	H	Pr^i	Ph	**18b**	98/2[d]	69 (51)	96 (99)	93/7 [d]	70 (54)	96 (99)
3	Ph	H	Me	4-MeC_6H_4	**18c**	70/30[d]	52 (41)	89 (99)	93/7	92	98
4	Ph	H	Me	4-FC_6H_4	**18d**	89/11[d]	74 (60)	97 (99)	92/8	88	99
5	Ph	H	Me	2-BrC_6H_4	**18e**	76/24[d]	64	94	91/9 [d]	76	90
6	Ph	H	Me	3-BrC_6H_4	**18f**	81/19[d]	61	86	81/19 [d]	61	92
7	Ph	H	Me	4-BrC_6H_4	**18g**	85/15[d]	56	98	82/18	77	97
8	Ph	H	Me	2-Furyl	**18h**	68/32[d]	50	92	84/16	77	98
9	Ph	H	Me	C_6H_{11}	**18i**	1/99	71 [e]	—[f]	50/50	33[c] 42 [e]	96 [f]
10	Ph	Me	Me	Ph	**18j**	21/79[d]	14[c] 63[e]	87 [f]	27/73	21[c] 69 [e]	92 [f]
11	Ph	Bu^i	Me	Ph	**18k**	92/8 [d]	46	97	35/65	21[c] 53 [e]	98 [f]
12	Ph	Bn	Me	Ph	**18l**	54/46[d]	42[c] 40[e]	98 [f]	50/50 [d]	33[c] 33 [e]	99 [f]
13	2-MeC_6H_4	H	Me	Ph	**18m**	56/44[d]	33	82	75/25 [d]	56	90
14	3-MeC_6H_4	H	Me	Ph	**18n**	76/24[d]	65	88	87/13	79 (66)	81 (90)
15	4-MeC_6H_4	H	Me	Ph	**18o**	94/6 [d]	79	92	88/12 [d]	60	94
16	4-(MeO)C_6H_4	H	Me	Ph	**18p**	93/7 [d]	81	96	90/10	75	92
17	4-FC_6H_4	H	Me	Ph	**18q**	88/12[d]	72	99	88/12	83	92
18	4-BrC_6H_4	H	Me	Ph	**18r**	91/9 [d]	77	99	94/6 [d]	83	98
19	2-Naphthyl	H	Me	Ph	**18s**	86/14[d]	70	85	80/20 [d]	66	75

[*] Chiral phosphoramidite **17** (0.05 mmol) and AgOTf (0.05 mmol) in dry toluene (3 mL) under argon atmosphere was added a solution of imino ester (1mmol) and nitroalkene (1 mmol) in toluene (5 mL). To the resulting suspension triethylamine (0.05 mmol, 7µL) was added and the mixture stirred at room temperature (20-30 °C) for 16-24 h. [a] From the crude product, determined by ^{1}H NMR. [b] Isolated yield (for the *exo*-adduct) after purification by flash chromatography. In brackets yields of the recrystallized *exo*-products. [c] For the *exo*-stereoisomer (HPLC). In brackets *ee* of the recrystallized samples. [d] Other stereoisomers were detected in noticeable proportions. [e] For de *endo*-**18** isomer. [f] The *endo*-**18** isomer was obtained as a racemic mixture.

The selective isolation of Michael-type addition compound **20** was possible by performing the reaction at lower temperatures followed by an acidic-basic treatment. This fact also supports the existence of a stepwise mechanism. The *syn*-diastereoselection was observed when silver benzoate was employed whilst the reaction in the presence of silver triflate failed. A comprehensive study of the reaction conditions was reported in Table 3, obtining the best results at -80 ºC (Table 3, entry 6). At this temperature equimolar amounts of compounds **18a** and *syn*-**20a** were generated. Cyclic product **18a** was obtained in 91:9 *exo:endo* ratio and 98% *ee* in 40% yield and the desired Michael-type adduct *syn*-**20a** was isolated in 40% yield as unique diastereoisomer and with a 98:2 *er*.

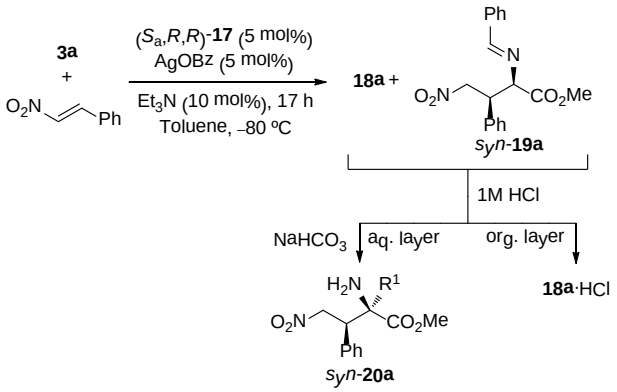


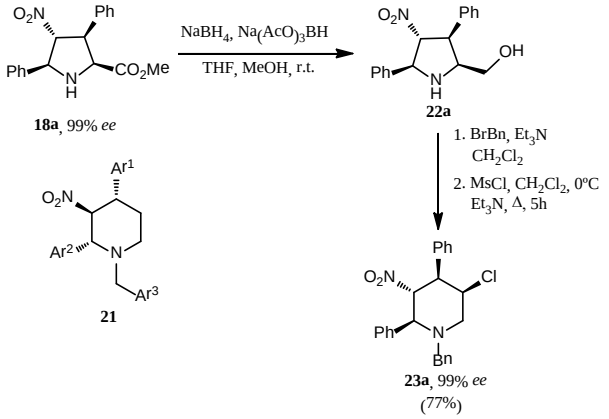
Table 3. Temperature dependent cycloadduct **18a**/Michael type adduct *syn*-**20** ratio.

			18a		**20a**		
en.	T (ºC)	**18a**/**19**	*exo/endo*[a]	er_{exo}[b]	yld[c] (%)	*syn/anti*[a]	er_{syn}[b]
1	24	>99:1	89/11	99:1	—	—	—
2	10	93:7	89/11	99:1	—	>99/1	98:2
3	0	88/12	89/11	99:1	—	>99/1	98:2
4	-40	72/28	89/11	99:1	—	>99/1	98:2
5	-60	63/37	90/10	99:1	33	>99/1	98:2
6	-80	50/50	91/9	99:1	40	>99/1	98:2

[a] From the crude product, determined by ^{1}H NMR. Other stereoisomers were detected in low proportions. [b] Determined by HPLC using chiral columns. [c] Isolated yield of the *syn*-isomer **20a** after flash chromatography (SiO_2).

We next focus our attention in a series of nitropiperidines **21**, which are potent farnesyl-

transferase inhibitors with promising antitumoral activity.[25] We envisaged that these products **21** can be accessed through the enantiomerically enriched proline derivatives **18** by a ring-expansion of their cyclic β-amino alcohol derivatives following the methodology developed by Cossy's group.[26] Thus, nitroalcohol **22a** (non purified) was obtained as optically pure compoud, in almost quantitative yield, after reduction with $NaBH_4/NaBH(AcO)_3$.[27] Finally, product **23a** could be synthesized in 77% overall yield by forming the tertiary amine with benzyl bromide and mesylation of the primary alcohol, taking place the corresponding ring expansion with complete retention of the configuration (Scheme 3).



Scheme 3. Synthetic approach to the potential farnesyltransferase inhibitor **23a** from enantiomerically enriched *exo*-nitroprolinate **18a**.

Conclusions

It has been demonstrated in this work the efficiency of chiral phosphoramidite·silver(I) salts to obtain diastereo- and enantioselectively *exo*-nitroprolinates through an unusual *exo*-1,3-DC of azomrthine ylides and nitroolefins. The reactions using methyl imino esters resulted to be much more clean and efficient and the scope of the reaction was very high. AgOBz and AgOTf derived chiral complexes are the best catalysts. However, for the Michael-type reaction only the AgOBz derived complex was effective at -80 ºC. These *exo*-nitroprolinates are appropriate precursors of potential farnesyltransferase inhibitiors by stereospecifice ring expansion.

Calculations demonstrated the blocking effect of the triflate anion over one prochiral face such as occurred in precedent 1,3-DC copper(II)-catalyzed reactions reported by us. Also, the interchange of the triflate anion by the nitro group in the reaction intermediate was not energetically favored at all.

Experimental Section

For experimental details, please see supporting information.

General Procedure for the 1,3-Dipolar Cycloaddition of Imino Esters and Dipolarophiles. To a solution of the chiral phosphoramidite **17** (0.05 mmol) and AgX (0.05 mmol) in dry toluene (3 mL) under argon atmosphere was added a solution of imino ester (1mmol) and nitroalkene (1 mmol) in toluene (5 mL). To the resulting suspension triethylamine (0.05 mmol, 7μL) was added and the mixture stirred at room temperature (20-30 °C) for 16-24 h (see main text). The crude reaction mixture was filtered through a small Celite path. The residue was purified by flash chromatography yielding pure *exo*-cycloadducts. Solid products were recrystallized in mixtures of *n*-hexane/ether.

General Procedure for the Synthesis of Michael-type addition product *syn*-20a. A solution of phosphoramidite (0.05 mmol) and $Cu(OTf)_2$ (0.05 mmol) in dry toluene (3 mL) was stirred for one hour prior to introduce the resulting colorless solution in a Dewar flask at –80 ºC . After 15 min was added a solution of imino ester **3a** (326 mg, 1 mmol) and nitrostyrene (149 mg, 1 mmol) in dry toluene (5 mL) and the reaction mixture was stirred over a period of 10 min. Then, triethylamine (0.05 mmol) was added and the mixture was stirred at this temperature for 17 hours. To the reaction crude was added HCl 0.1M (5 mL) at –80 ºC and then the reaction was allowed to reach room temperature. After stirring for one additional hour, the organic phase was extracted. The aqueous phase was neutralized with solid $NaHCO_3$ and the Michael product was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure affording pure compound *syn*-**20a**.

Synthesis of compound 21a. To a solution of the chiral *exo*-pyrrolidine **18a** (200 mg, 0.613 mmol) in dry THF (10 mL) under an argon atmosphere at room temperature, $NaBH_4$ (94 mg, 2.5 mmol) and $NaB(OAc)_3H$ (25 mg, 0.12 mmol) were sequentially added. To the resulting white slurry was added dry methanol (157μL, 5 mmol) and the mixture was stirred until complete disappearance of starting material (72 hours, observed by TLC). The mixture was quenched with a saturated solution of NH_4Cl (15 mL) and the organic solvents were evaporated under reduced pressure. Then, the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was not purified and immediately used for the next transformation. To a solution of the amino alcohol **22a** (40 mg, 0.134 mmol) in CH_2Cl_2 (2 mL), BnBr (20 μL, 0.162 mmol) and Et_3N (38 μL, 0.268 mmol) were successively added. The reaction media was stirred under reflux for 16 h before being cooled. Then solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (hexane/EtOAc 95/5 to 70/30) to afford the tertiary amine which was dissolved in CH_2Cl_2 (5 mL) at 0ºC. Et_3N (77 μL, 0.5 mmol) and mesyl chloride (35 μL, 0.44 mmol) were carefully added in this order. After stirring at reflux for 5 h, H_2O was added to the reaction mixture. Then the

aqueous was extracted with CH_2Cl_2 and the organic layer dried with $MgSO_4$, filtered, and concentrated under reduced pressure. After purification by flash chromatography on silica gel (hexane/EtOAc 95/5 to 70/30) **23a** was isolated as yellow oil (42 mg, 77% yield).

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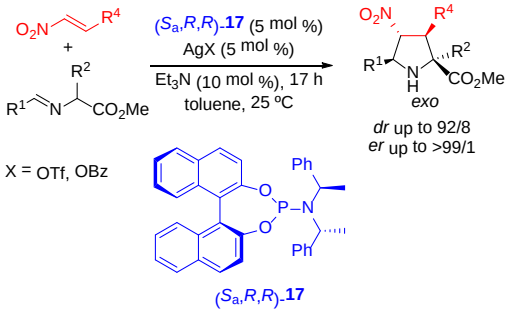
FULL PAPER

Efficient Diastereo- and Enantioselective Synthesis of *exo*-Nitroprolinates by 1,3-Dipolar Cycloadditions Catalyzed by Chiral Phosphoramidite·Silver(I) Complexes



Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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