Enantioselective synthesis of polysubstituted spiro-nitroprolinates mediated by a (*R*,*R*)-Me-DuPhos·AgF-catalyzed 1,3-dipolar cycloaddition

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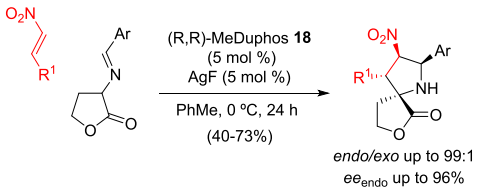


ABSTRACT: The synthesis of constrained spirocycles is achieved effectively by means of 1,3-dipolar cyclodditions employing α-imino γ-lactones as azomethine ylide precursors and nitroalkenes as dipolarophiles. The complex formed by (*R*,*R*)-Me-DuPhos **18** and AgF is the most efficient bifunctional catalyst. Final spiro-nitroprolinates cycloadducts are obtained in good to moderate yields and both high diastereo- and enantioselections. Density functional theory (DFT) calculations supported the expected absolute configuration as well as other stereochemical parameters.

The importance of having a wide number of enantiomerically enriched sterically congested polysubstituted organic compounds is continuously increasing. Many scientific areas need all these functionalized structures for their specialized researches. Along this line, optically active polysubstituted nitroprolinates have emerged since 2005 as promising therapeutic agents.[1] For example, molecules **1** (Figure 1) are important inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma and in a murine model of colon carcinoma metastasis, as well as potent antiadhesive properties in several cancer cell lines.[2,3] Bicyclic heterocycles **2**, containing an atropane scaffold have been found as novel inhibitors of skin cancer.[4] Spirooxindoles **3** increased the mortality of zebrafish embryos[5] whilst molecules **4** with benzopyran skeleton were successfully tested as antimycobacterials against *M. tuberculosis* H37Rv strain.[6] Besides, the most simple 4-nitroprolines *exo*-**5**, and *endo*-**6** have been recently used as chiral organocatalysts in aldol reactions.[7] Michael-type addition of ketones to nitroalkenes was successfully run in the presence of *exo*-**5b** (X=H),[8] obtaining good to excellent diastereoselections and high enantiomeric ratios. A family of enantiopure tetrasubstituted nitroprolinate surrogates has been designed as scaffolds for proteasome inhibitors with high medicinal prospects.[9] In addition, the NH-D-EhuPhos ligand **6** has been efficiently employed in the 1,3-dipolar cycloadditions (1,3-DC)[10] to yield nitroprolines and structurally rigid spiro-compounds from chiral γ-lactams.[11,12]

Grigg and co-workers reported in 2008 the silver-promoted racemic and diastereoselective 1,3-DC involving homoserine derived imino esters **7**[13] and nitroalkenes **8** obtaining spirolactones **9** as major products (Scheme 1).[14] The asymmetric approach to this molecules was performed by the employment of organocatalysts. Michael adducts could be isolated in a first step. A second treatment with DBU afforded enantiomerically enriched *endo*-cycloadducts **9** in good yields.[15] These homoserine-lactone surrogates are a class of signaling molecules involved in the so called bacterial quorum sensing.[16]

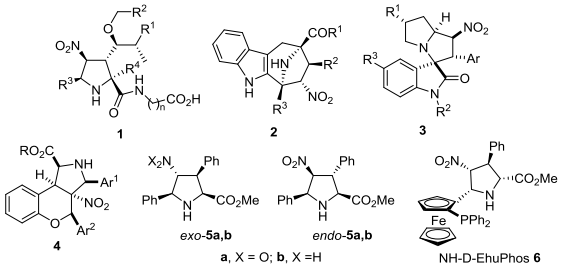


Figure 1. Nitroprolinates with synthetic or biological applications.

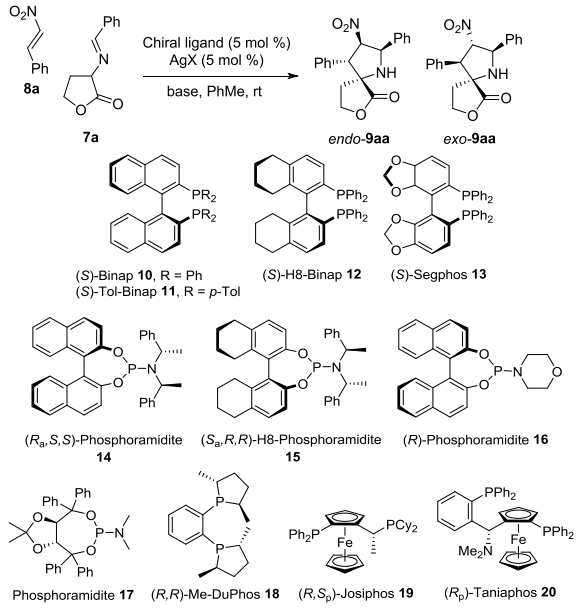
Scheme 1. Racemic 1,3-DC between iminolactones **7** and nitroalkenes **8.**

In this work, with the idea of combining structural rigidity and enantiomerically enriched nitroprolinates, we report the direct enantioselective synthesis of these attractive intermediates **9**.[17,18,19]

For the optimization of the reaction privileged ligands[20] **11-20** were tested in the silver-catalyzed 1,3-DC between imino lactone **7a** and β-nitrostyrene **8a**. Although we used L-homoserine lactone as starting material to prepare dipole precursors **9**, the chiral information contained in these compounds is not relevant (*vide infra*). (*S*)-Segphos **13**, (*S*)-Binap **10** and

its derivatives **11** and **12** afforded very low enantiomeric ratios (although high diastereoselectivity) of the major *endo*-cycloadduct *ent*-**9aa** AgTfa (Tfa = trifluoroacetate) and AgF[21] being the most appropriate silver(I) salts (Table 1, entries 1-6). Then, phosphoramidites **14**-**17** were next evaluated. When the reaction was run in the absence of triethylamine using the (R_a,*S*,*S*)-**14**·AgF complex better results were recorded (Table 1, entries 7 and 8). Another silver salts in combination with phosphoramidite **14**, useful in other 1,3-DC with nitroalkenes,[22] such as AgOTf, AgOBz, and AgOAc and Ag_2CO_3[23] were assayed but never improved the results obtained with AgF (Table 1, entries 9-15). Other phosphoramidites **15**-**17** gave poor enantioselectivities (Table 1, entries 13-15). However, (*R*,*R*)-Me-DuPhos **18**·AgF complex furnished *endo*-**9aa** in 99:1 dr and 86:14 er. Chiral ferrocenyl ligands **19** and **20** did not give better results (Table 1, entries 16-18). The effect of the temperature was considered and the enantiomeric ratio could be increased up to 90:10 when the reaction was performed at 0 ºC rather than when the reaction was carried out at -20 ºC (Table 1, entries 19 and 20). It is remarkable the high *endo*:*exo* ratio achieved in entry 16 of Table 1 (99:1) *versus* the 3:1 reported in the literature for the racemic mixture.[14]

Table 1. Optimization of reaction conditions of 1,3-DC of **7a** and **8a**



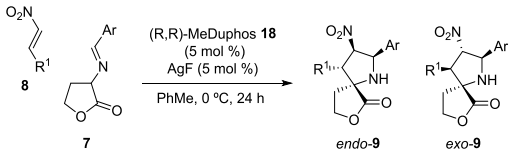
en.	ligand	AgX	base	conv (%)[a]	endo:exo[a]	er[b,c]
1	(*S*)-**10**	AgTfa	TEA	>98	93:7	45:55
2	(*S*)-**10**	AgF	TEA	>98	89:11	45:55
3	(*S*)-**10**	AgTfa[c]	TEA	>98	93:7	36:64
4	(*S*)-**11**	AgF	TEA	>98	96:4	50:50
5	(*S*)-**12**	AgF	TEA	>98	98:2	31:69
6	(*S*)-**13**	AgF	TEA	>98	98:2	20:80
7	(R_a,*S*,*S*)-**14**	AgF	TEA	>98	88:12	73:27
8	(R_a,*S*,*S*)-**14**	AgF	—	>98	90:10	78:22
9	(R_a,*S*,*S*)-**14**	AgOTf	—	>95	84:16	66:34
10	(R_a,*S*,*S*)-**14**	AgOBz	—	>98	91:9	65:35
11	(R_a,*S*,*S*)-**14**	AgOAc	—	>98	86:14	66:34
12	(R_a,*S*,*S*)-**14**	Ag_2CO_3	—	>98	92:8	70:30
13	(S_a,*R*,*R*)-**15**	AgF	—	>98	76:24	36:64
14	(*R*)-**16**	AgF	—	>98	99:1	70:30
15	**17**	AgF	—	>95	92:8	37:63
16	(*R*,*R*)-**18**	AgF	—	>95	99:1	86:14
17	**19**	AgF	—	>95	79:21	66:34
18	**20**	AgF	—	>20	—	—
19	(*R*,*R*)-**18**	AgF[d]	—	>95	99:1	90:10
20	(*R*,*R*)-**18**	AgF[e]	—	>90	99:1	88:12

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Determined by HPLC using chiral coated columns, *endo*-**9aa**:*ent*-**9aa** er. [c] Reaction performed at -50 ºC during 50 h. [d] Reaction performed at 0 ºC during 50 h. [e] Reaction performed at -20 ºC.

The possible structure of the catalyst involved in the process was studied. For a 1:1 mixture of (*R*,*R*)-Me-DuPhos **18** and AgF, ^{31}PNMR experiment (in deuterated chloroform) revealed two doublets at 22.66 ppm (J_{Ag109} = 256 Hz and J_{Ag107} = 222 Hz) and ESI-MS afforded a M^+ = 719 corresponding to (**18**)$_2$·Ag cluster. Analogous ^{31}P NMR and ESI-MS spectra were recorded when a 2:1 mixture of (*R*,*R*)-Me-DuPhos **18** and AgF was prepared. Another ^{31}PNMR experiment was performed by addition of **7a** to the preformed 1:1 complex (*R*,*R*)-Me-DuPhos **18**:AgF but no signals were detected at all. At this point, we performed the reaction of the entry 16 of the Table 1 with the (**18**)$_2$·AgF complex generated *in situ*. The reaction was very slow and almost racemic *endo*-**9aa** was obtained with less than 5% conversion after 1 d.

The scope of the reaction was next investigated. The (*R*,*R*)-Me-DuPhos **18** and AgF[24] were mixed and stirred for 30 min and the imino ester **7** was added at 0 ºC followed by the nitroalkene **8**. Unsubstituted and 2, 3, or 4-substituted aryl groups of the nitrostyrene molecule afforded in relative good yields (45-54%) **9ac**-**ae** cycloadducts with high diastereoselectivity and moderate to high enantiomeric ratios (Table 2, entries 1-4). 2-Furyl derivative **8e** and alkyl substituted nitroalkenes **8f-g** afforded higher er and good chemical yields with modest diastereoselection (Table 2, entries 5-7). In these examples run with alkylated nitroolefins, the diastereoselection was higher than the 1:1 obtained in the literature.[14] A modification of the aryl group of imino lactone **7** gave, in general similar chemical yields, and higher both diastereomeric and enantiomeric ratios of products **9** (Table 2, entries 8-15). 2-Methylphenyl surrogate **7b** was also an appropriate precursor giving **9ba** as only one diastereoisomer although with a low enantiomeric ratio (80:20, Table 2, entry 8).

Table 2. Scope of the enantioselective 1,3-DC of **7** and nitroalkenes **8**



en.	**7**, Ar	**8**, R^1	**9**	yield (%)[a]	endo/ exo[b]	er[c,d]
1	**7a**,Ph	**8a**, Ph	**9aa**	65	99:1	90:10
2	**7a**, Ph	**8b**, 4-FC_6H_4	**9ab**	45	99:1	80:20
3	**7a**, Ph	**8c**, 2-BrC_6H_4	**9ac**	50	95:5	75:25
4	**7a**, Ph	**8d**, 3-BrC_6H_4	**9ad**	54	95:5	95:5
5	**7a**, Ph	**8e**, 2-Furyl	**9ae**	71	99:1	92:8
6	**7a**, Ph	**8f**, Cy	**9af**	65	78:22	96:4
7	**7a**, Ph	**8g**, Bu^i	**9ag**	68	74:26	93:7
8	**7b**, 2-MeC_6H_4	**8a**, Ph	**9ba**	50	95:5	75:25
9	**7c**, 3-MeC_6H_4	**8a**, Ph	**9ca**	73	95:5	93:7
10	**7d**, 4-MeC_6H_4	**8a**, Ph	**9da**	51	99:1	93:7
11	**7e**, 4-$MeOC_6H_4$	**8a**, Ph	**9ea**	52	97:3	94:6
12	**7f**, 4-BrC_6H_4	**8a**, Ph	**9fa**	40	99:1	98:2
13	**7g**, 2-Naphthyl	**8a**, Ph	**9ga**	45	99:1	93:7
14	**7h**, 2-Furyl	**8a**, Ph	**9ha**	51	99:1	80:20

[a] Isolated yield after purification (flash silica gel). [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC using chiral coated columns. [d] Values for compounds *endo*-**9**.

Theoretical calculations within the density functional theory (DFT) framework[25] were carried out in order to further assess

the origins of the observed enantio- and diastereoselectivity in the 1,3-DC of **7a** and nitroalkene **8** catalyzed by (*R*,*R*)-MeDuPhos **18**·AgF. This latter computational method has been demonstrated to be an useful tool for the analysis of the stereochemical outcome observed in 1,3-DC, especially in reactions catalyzed by chiral silver(I) complexes.[19b,23b,26] Moreover, we demonstrated in previous works that the enantioselectivity stems from the coordination pattern in the azomethine ylide and the effective blockage of one of the prochiral faces by the chiral ligand in the initial reactive complex.[27]

Our calculations on the initial N-metalated **INT1** reactive complex show that the silver(I) atom presents a tetrahedral environment where coordination sphere is saturated by the carbonylic oxygen atom and the nitrogen atom of the azomethine ylide and the two phosphorous atoms of the ligand **18** (see Supporting Information). This coordination pattern implies an effective blockage of the (1*Si*,3*Re*) prochiral face, thus prompting the preferential formation of cycloadducts *endo*-**9** and *exo*-**9** over its enantiomeric counterparts *ent-endo*-**9** and *ent-exo*-**9**. At this stage the chiral information contained in the α-amino-γ-butyrolactone moiety is destroyed because of the formation of the azomethine ylide. Therefore, any source of chiral information relies on the chiral ligand (Figure 3).

Exploration of the Gibbs free energy surface shows that these 1,3-DC are not concerted but stepwise.[28] The first step consists of a Michael-type nucleophilic attack on the α,β-unsaturated nitro derivative to yield an intermediate **INT2** that leads to formation of the corresponding cycloadduct by an intramolecular Mannich-like ring closure step. The main geometric features and relative energies of the stationary points corresponding to the first step of the 1,3-DC between **7a** and nitroalkene **8a** catalyzed by (*R*,*R*)-MeDuPhos **18**·Ag are gathered in Figure 2.

Our results showed that **TS1** and **TS2**, associated with the formation of cycloadduct *endo*-**9** and its enantiomer *ent-endo*-**9**, are less energetic than **TS3** and **TS4** (associated with formation of *exo*-**9** and *ent-exo*-**9**) due to a favorable Coulombic interaction between the nitro moiety of **8** and the silver atom in the formers. This favorable interaction, associated with an *endo* approach, results in a theoretical diastereomeric *endo*-**9**:*exo*-**9** ratio of 99:1, which is in good agreement with the experimental results (Table 2, entry 1). Moreover, the effective blockage of the (1*Si*,3*Re*) prochiral face by the catalytic system is compatible with the energetic difference of 1.8 kcal/mol between **TS1** and **TS2**. This difference in favor of **TS1** is related to the lower energy required to deform the geometry of the complex formed by the chiral ligand **18** and the *N*-metalated azomethine ylide. This initial geometry is modified to that of the TS. In addition, this geometry change minimizes the TS steric repulsion between the incoming nitroalkene and the catalytic system. This computed energetic difference is associated with a theoretical er of 96:4, also in perfect agreement with the experimental evidences.

The complete reaction mechanism that yields the cycloadduct **9aa** was further analyzed. The main geometrical features of the second transition structure **TS5** and the energetic profile are depicted in Figure 3. The computed Gibbs activation barrier associated with the second step was ca. 7 kcal/mol lower than that associated with the first step. However, formation of the major cycloadduct is slightly endergonic. Therefore, the final equilibrium is the driving force of the reaction because ensures the release of **9aa** and the recovery of the reactive ylide complex.

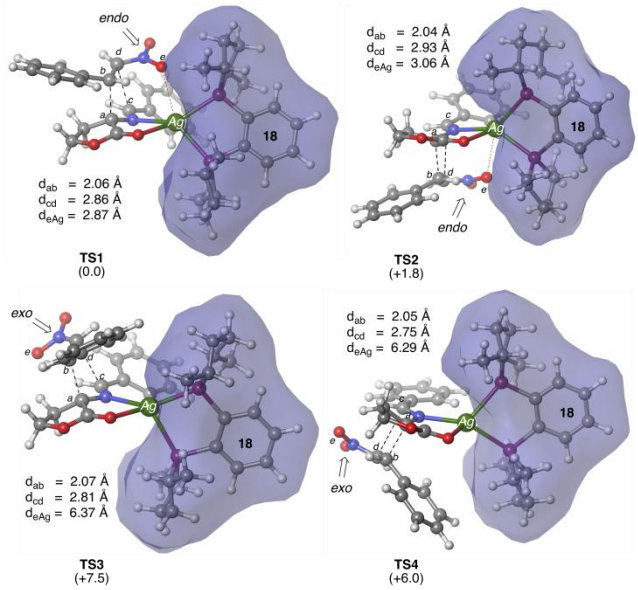


Figure 2. Main geometric features and relative energies (in kcal/mol) of the computed transition structures associated with the first step of the reaction between **8** and azomethine ylide (R,R)-MeDuPhos-Ag·**7a** computed at the M06(PCM)/6-31G*&LanL2DZ//B3LYP(PCM)/6-31G* &LanL2DZ level of theory. Bond lengths are given in Å. Blue surfaces represent the solvent-accessible surface with a probe radius of 1.9 Å.

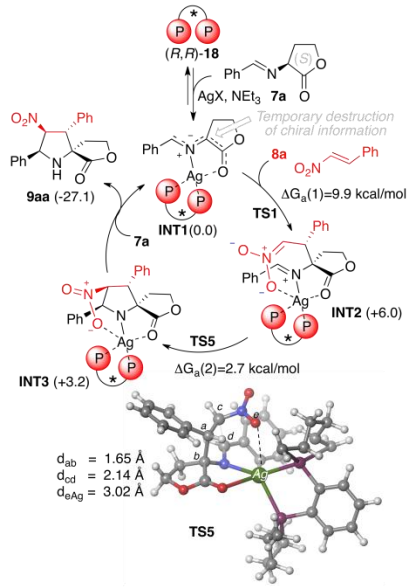


Figure 3. Main geometric features of the second transition structure and relative energies (in kcal/mol) of the profile associated with the reaction between **8** and azomethine ylide **INT1** to yield **9aa** computed at the M06(PCM)/6-31G*&LanL2DZ//B3LYP(PCM)/6-31G*&LanL2DZ level of theory. Bond lengths are given in Å.

The relative configuration of major stereoisomers *endo*-**9** deduced by NOE experiments and by correlation with the chemical shifts and coupling constants previously reported for the racemic products,[14] were in agreement with the absolute configuration revealed by both the most favored computed structure and by X-ray diffraction analysis of compound *endo*-**9ga**.[29]

In conclusion, an efficient method for the synthesis of spiranic cycloadducts *endo*-**9** from α-imino γ-lactones has been achieved. (*R*,*R*)-MeDuPhos **18**·AgF was the most efficient in acting as bifunctional catalyst because the fluoride is behaving

as base. The *endo*-diastereoisomers were obtained in both high enantiomeric and diastereomeric ratios. These *endo*-products are unusual in this type of cycloaddtitions promoted by chiral Lewis acids.[30] DFT calculations resulted to be a crucial tool to clarify the absolute configuration of these cycloadducts, which was confirmed later by X-ray diffraction analysis.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: Experimental details, characterization data, and NMR spectra for new compounds (PDF), computational data and X-RD analysis.

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