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

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201####. ((Please delete if not appropriate))

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) involving azomethine ylides and electrophilic alkenes was described in 2002 using chiral bisphosphine·silver(I) and zinc(II) 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.

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, 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 have been used as leukocyte function associated antigen-1 antagonists during a cancer evolution, with important activity as inhibitors of α4β1-integrin-mediated hepatic melanoma metastasis and even for treatments of other diseases. More simple exo-nitroprolinates have shown a high efficiency as organocatalysts in asymmetric aldol reactions.

1

2
diastereoselective 1,3-DC of iminoesters approaches \[15\] at their most favorable TS. exo-metal complexes showed preferential enantioselective 1,3-DC.

Fukuzawa’s group reported a highly effective imino esters asymmetric cycloaddition using glycine derived efficient silver(I) catalyzed enantio- and copper(I) gold(I) complexes. These metal complexes showed preferential exo-approaches\[15\] at their most favorable TS.

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,\[16\] it was curious not to find any efficient 1,3-DC with \(\beta\)-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 phosphoramidite 17 (Figure 3).

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\[18\] catalyzed the 1,3-DC of a malonate derivative (3, \(R^1 = CO_2Et\)).\[19\] The major contributions using \(\alpha\)-amino esters derived imines were achieved under the control of chiral Lewis acids\[10\] formed by copper(II) \[6-9\] and nickel(II) \[13\] complexes. These metal complexes showed the control of chiral Lewis acids \[10\] formed by silver(I)·thioclickferrophos complexes 18a.

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 \textit{in situ} generation of the corresponding 17-silver(I) complex (5 mol% as optimal catalyst loading, 30 min, toluene at 25 \(^\circ\)C). 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\(_2\)O, 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

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

Figure 3. Chiral privileged ligands.

\(\begin{align*}
N, PPh_2, PPh_2, CO_2R_2, \text{PPh}_2, Ph, PPh_2, \text{diastereoselective 1,3-DC of iminoesters}, \text{at their most favorable TS. exo-metal complexes showed preferential enantioselective 1,3-DC.}
\end{align*}\)
in HPLC using chiral columns and comparison with the data obtained for the same known product. \cite{12b}

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>MX</th>
<th>Conv. [%]</th>
<th>$\text{exo}$/$\text{endo}$</th>
<th>ee [%]</th>
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<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>AgClO$_4$</td>
<td>5</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>AgClO$_4$</td>
<td>45</td>
<td>54/46$^{[a]}$</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>AgClO$_4$</td>
<td>&gt;95</td>
<td>10/94</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>AgOAc</td>
<td>&gt;95</td>
<td>90/10$^{[a]}$</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>AgOTFA</td>
<td>&gt;95</td>
<td>70/30$^{[a]}$</td>
<td>89</td>
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<tr>
<td>6</td>
<td>17</td>
<td>AgOBz</td>
<td>&gt;95</td>
<td>91/9</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>ent-17</td>
<td>AgOBz</td>
<td>&gt;95</td>
<td>91/9</td>
<td>-96</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>AgOTf</td>
<td>&gt;95</td>
<td>90/10$^{[a]}$</td>
<td>96</td>
</tr>
<tr>
<td>9$^{[e]}$</td>
<td>17</td>
<td>Cu(OTf)$_2$</td>
<td>95</td>
<td>89/11</td>
<td>99</td>
</tr>
</tbody>
</table>

$^{[a]}$ Unless otherwise specified: ligand (5 mol%), MX (5 mol%), 3a (0.2 mmol), β-nitrostyrene (0.2 mmol), Et$_3$N (5 mol%) in toluene (2 mL), rt for 17 h.

$^{[b]}$ From the crude product, determined by $^1$H NMR.

$^{[c]}$ For the major exo-stereoisomer.

$^{[d]}$ Other stereoisomers were detected in low proportions.

$^{[e]}$ Reference 12b

In order to gain a better understanding of these experimental results and, in particular, the origins of the unexpected $\text{exo}$-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,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.\cite{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.\cite{12b}

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.\cite{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 2Si,5Re-face in the most stable ylide [(S,R,R)-17·AgOTf-II].

These computational results are compatible with $^1$F-NMR experiments on Cu(OTf)$_2$ and AgOTf complexes of (S,R,R)-17 and imine 3a in

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Figure 4. Structures and relative energies (in kcal mol$^{-1}$) of complexes derived from imine 3a and (A) (S,R,R)-17·Cu(OTf)$_2$ and (B) (S,R,R)-17·AgOTf at M06/LANLDZ/ONIOM(B3LYP/LANLD2DZ:UFF)+ΔZPCE 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.
the absence of base. In the case of Cu(OTf)₂, the $^{19}$F signals appears at $\delta$ -78.04 ppm, whereas when AgOTf the CF₃ resonance is observed at $\delta$ -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 (Sₐ,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 (Sₐ,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 (Sₐ,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 (Sₐ,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 \(c.a. 5 \text{ kcal mol}^{-1}\). It is noteworthy that 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 \(\text{exo-18a}\), that is highly exothermic \(\Delta_{\text{rxn}} G(3) = 11.8 \text{ kcal mol}^{-1}\) thus ensuring the recovery of the reactive ylide complex.

The scope of the reaction was made with different nitroalkenes, \(\alpha\)-amino esters and benzylidene 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 \(\text{exo-diastereoselection}\) for the isopropyl ester. However, the lower yield of the \(\text{exo/endo}\) 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 \(^1H\) 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, \(\text{exo-diastereoselectivities}\) and enantioselections in products 18 when the reactions occurred in the presence of \((S, R, R)-\text{AgOTf}\) 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% \(\text{ee}\) of \(\text{exo-18h}\) (Table 2, entry 8). In general, better results were obtained with \((S, R, R)-\text{AgOBz}\) than with \(\text{Cu(OTf)}_2\). When the nitroalkene incorporated an aliphatic cyclohexyl group a reversal diastereoselectivity was observed in the \(\text{17-AgOTf}\) catalyzed 1,3-DC. The exclusive \(\text{endo}\) isomer was isolated in 71% yield but as a racemic mixture. However, an equivmolar mixture of \(\text{endo/exo}\) diastereoisomers in 75% overall yield in the analogous reaction performed with AgOBz. Again, the adduct \(\text{endo-18i}\) was isolated as a raceme, whilst the \(\text{exo}\)-isomer 18j was obtained in low 32% yield but with a 96% \(\text{ee}\) (Table 2, entry 9). On the other hand the 1,3-DC with this nitroalkene failed with the \(\text{Cu(OTf)}_2\) complex 11.\(^{[12b]}\)

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

With respect to the use of different methyl benzylideneimino glycines The more sterically hindered \(o\)-tolyl imino group also favoured the generation of the \(\text{endo-isomer 18m}\) but in less proportion in the case of AgOBz than with \(\text{Cu(OTf)}_2\). On the other hand, the \(\text{exo-18m}\) was obtained in a ee up to 90% with AgOBz towards 54% ee with \(\text{Cu(OTf)}_2\) (Table 2, entry 13). It seems that the lower steric repulsion the higher proportion of \(\text{exo-adduct and enantioselections}\). 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 diastereoselections, 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 \(\text{Cu(OTf)}_2\). Finally in the case of the 2-naphthyl substituent, \(\text{exo-18s}\) was obtained with up to 72% \(\text{de}\) and 85% \(\text{ee}\) when AgOTf was used better than \(\text{Cu(OTf)}_2\) and AgOBz (Table 2, entry 19).

**Table 2.** Scope of the diastereo- and enantioselective 1,3-DC between imino esters 3 and nitroalkenes catalyzed by \((S, R, R)-\text{AgOTf}\) or \((S, R, R)-\text{AgOBz}\).\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>(\text{18})</th>
<th>((S, R, R)-\text{AgOTf})</th>
<th>((S, R, R)-\text{AgOBz})</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(\text{exo/}^{[a]})</td>
<td>(\text{Yield}^{[b]})</td>
</tr>
<tr>
<td>1</td>
<td></td>
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<td>(\text{endo}^{[a]})</td>
<td>51%</td>
</tr>
<tr>
<td>2</td>
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<td></td>
<td></td>
<td></td>
<td>(\text{endo}^{[a]})</td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(\text{exo/}^{[a]})</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(\text{exo/}^{[a]})</td>
<td>96%</td>
</tr>
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</table>

\(^{[a]}\) \text{Scheme 2. Scope of the diastereo- and enantioselective 1,3-DC between imino esters 3 and nitroalkenes catalyzed by \((S, R, R)-\text{AgOTf}\) or \((S, R, R)-\text{AgOBz}\).}\n
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\(^{[b]}\) \text{Yield} = \text{Yield of the isolated product determined by 1H NMR), (Table 2, entries 2-9).}

\(^{[c]}\) \text{ee} = \text{enantiomeric excess obtained in the crude mixture of the isolated product, (Table 2, entries 3-18).}
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, obtaining the best results at -80 °C (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 cycladduct 18a/Michael type adduct syn-20 ratio.

<table>
<thead>
<tr>
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<tr>
<td>1</td>
<td>24</td>
<td>89:11</td>
<td>99:1</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>2</td>
<td>10</td>
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<td>99:1</td>
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<td>3</td>
<td>0</td>
<td>88:12</td>
<td>99:1</td>
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<tr>
<td>4</td>
<td>-40</td>
<td>72:28</td>
<td>99:1</td>
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<td>63:37</td>
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<td>50:50</td>
<td>99:1</td>
<td>40</td>
<td>99:1</td>
<td>98:2</td>
</tr>
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</table>

| 18a  | 90/10[1] | 80 (65) | 96 (99) | 91/9 | 88 | 99 |
| 18b  | 98/2[4] | 69 (51) | 96 (99) | 93/7 | 70 (54) | 96 (99) |
| 18c  | 70/30[6] | 52 (41) | 89 (99) | 93/7 | 92 | 98 |
| 18d  | 89/1[6] | 74 (60) | 97 (99) | 92/8 | 88 | 99 |
| 18e  | 76/24[6] | 64 | 94 | 91/9 | 76 | 90 |
| 18f  | 81/19[6] | 61 | 86 | 81/19 | 61 | 92 |
| 18g  | 85/15[6] | 56 | 98 | 82/18 | 77 | 97 |
| 18h  | 68/32[6] | 50 | 92 | 84/16 | 77 | 98 |
| 18i  | 1/99[6] | 71 | - | 50/50 | 33 | 96 |
| 18j  | 21/79[6] | 14 | 63 | 27/73 | 21 | 92 |
| 18l  | 54/46[6] | 42 | 98 | 50/50 | 33 | 99 |
| 18m  | 56/44[6] | 33 | 82 | 75/25 | 56 | 90 |
| 18n  | 76/24[6] | 65 | 88 | 87/13 | 79 | 91 (90) |
| 18o  | 94/6[4] | 79 | 92 | 88/12 | 60 | 94 |
| 18p  | 93/7[4] | 81 | 96 | 90/10 | 75 | 92 |
| 18q  | 88/12[6] | 72 | 99 | 88/12 | 83 | 92 |
| 18s  | 86/14[6] | 70 | 85 | 80/20 | 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 1H 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 yield 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.

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 compound, in almost quantitative yield, after reduction with NaBH₄/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 phosphoramidate-silver(I) salts to obtain diastereo- and enantioselectively exo-nitroprolinates through an unusual exo-1,3-DC of azomethine 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 °C. These exo-nitroprolinates are appropriate precursors of potential farnesyltransferase inhibitors by stereospecific 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 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 °C. 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 °C 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 NaHCO₃ and the Michael product was extracted with ethyl acetate. The organic layers were combined, dried over MgSO₄ 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, NaBH₄ (94 mg, 2.5 mmol) and NaB(OAc)₃-H (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 NH₄Cl (15 mL) and the organic solvents were evaporated under reduced pressure. Then, the aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic phases were dried over MgSO₄ 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 CH₂Cl₂ (2 mL), BnBr (20 μL, 0.162 mmol) and Et₂N (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 product was purified by flash chromatography (hexane/EtOAc 95/5 to 70/30) to afford the tertiary amine which was dissolved in CH₂Cl₂ (5 mL) at 0°C. Et₂N (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, H₂O was added to the reaction mixture. Then the...
aqueous was extracted with CH$_2$Cl$_2$ 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).

Acknowledgements

This work has been supported by the Spanish Ministerio de Ciencia e Innovación (MICINN) (Consolider INGENIO 2010 CSD2007-00006, CTQ2010-20387), FEDER, Generalitat Valenciana (PROMETEO/2009/039), and by the University of Alicante. L. M. C. thanks the MICINN for a FPI fellowship. Financial support was provided by the Ministerio de Economía y Competitividad (MINECO) of Spain and FEDER (projects CTQ2010-16959/BQU, and Consolider-Ingenio CSD2007-00006), the University of the Basque Country (UPV/EHU, UFI11/22 QOSYC), the Basque Government (GV/EJ, grant IT-324-07). The authors thank the SGI/IZO-SGIker UPV/EHU and the DIPC for generous allocation of computational resources.
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[14] The exo descriptor refers the approach of the dipolarophile in which the electron-withdrawing group of the 1,3-dipole and the nitro group are arientated in the oposite direction.


[26] A similar reduction was performed in the presence of NaBH₄/Na(MeO)₃BH instead of NaBH₄/Na(AcO)₃BH: J. A.
Efficient Diastereo- and Enantioselective Synthesis of \( \text{exo} \)-Nitropolinates by 1,3-Dipolar Cycloadditions Catalyzed by Chiral Phosphoramidite·Silver(I) Complexes

\[
\begin{align*}
\text{R}^1\text{N} = \text{CO}_2\text{Me} & \quad \text{AgX} (5 \text{ mol } \%) \\
\text{R}^2 \quad \text{Et}_3\text{N} (10 \text{ mol } \%) & \quad 17 \text{ h} \\
\text{toluene, 25 } ^\circ\text{C} & \\
\text{dr up to 92/8} & \quad \text{er up to } >99/1
\end{align*}
\]

\[X = \text{OTf, OBz}\]