ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 4649

Received 5th March 2013,
Accepted 26th March 2013

DOI: 10.1039/c3cc41663a

www.rsc.org/chemcomm

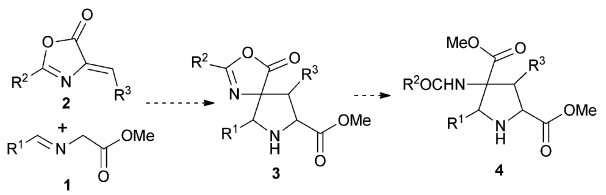
Enantioselective synthesis of 4-aminopyrrolidine-2,4-dicarboxylate derivatives *via* Ag-catalyzed cycloaddition of azomethine ylides with alkylidene azlactones†

María González-Esguevillas, Javier Adrio* and Juan C. Carretero*

A catalytic highly enantioselective silver–DTBM-segphos catalyzed cycloaddition of α-iminoesters with alkylidene azlactones is reported. This procedure provides an effective access to 4-amino-pyrrolidine-2,4-dicarboxylate derivatives with high diastereo- and enantioselectivity.

The pyrrolidine ring is considered to be a privileged structure in medicinal chemistry since its derivatives are valuable scaffolds for the discovery of new therapeutic agents.[1] In particular, proline derivatives having a quaternary stereocenter have been broadly studied in peptidomimetic chemistry since their introduction into peptides restricts the conformational flexibility of the peptidic chain, and may increase its selectivity and metabolic stability.[2] Furthermore, proline analogues have been widely used as chiral synthons and catalysts in organic synthesis.[3]

In this context, 4-aminopyrrolidine-2,4-dicarboxylate derivatives **4** (Scheme 1) are valuable multipurpose products. For instance, examples of these compounds have been identified as potent, highly selective agonists for metabotropic glutamate receptors, which are involved in the pathologies of several neurodegenerative diseases.[4] In addition, 4-aminopyrrolidine-2,4-dicarboxylate has been used as a monomer for the preparation of non-natural oligomers with well-defined three-dimensional structures.[5]



Scheme 1

The existing synthetic methods for the enantioselective preparation of 4-amino 4-carboxylate proline derivatives usually consist of multistep sequences starting from enantiopure starting materials.[6] Therefore, the development of more convergent synthetic strategies, which facilitate the preparation of this kind of cyclic amino acids, is desirable.

Among the procedures reported for the enantioselective preparation of highly substituted pyrrolidines, the metal catalyzed 1,3-dipolar cycloaddition of azomethine ylides with activated olefins has emerged as one of the most powerful methodologies.[7] In recent years an extensive effort in this area has led to the development of a plethora of catalytic systems which have efficiently extended the scope of the reaction with regard to both the dipole and dipolarophile partners.[8] Very recently a few examples of the application of this methodology to the construction of spirocyclic pyrrolidines have been reported.[9]

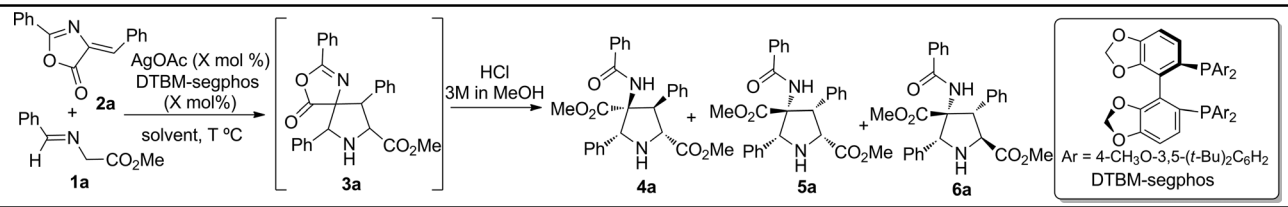
We envisioned that proline analogues with amino acid substitution at C-4 could be rapidly assembled in a modular and highly selective manner *via* 1,3-dipolar cycloaddition between α-iminoesters and the appropriate olefinic azlactones as dipolarophiles (Scheme 1). Nevertheless, this kind of alkene has been scarcely applied in 1,3-dipolar cycloadditions,[10] and to the best of our knowledge, there are no precedents of their use as dipolarophiles in catalytic asymmetric 1,3-dipolar cycloadditions of azomethine ylides.

In order to evaluate the viability of the process, we chose the cycloaddition of the iminoester **1a** with benzylidene azlactone **2a** as a model reaction. After screening a variety of metal salts and chiral ligands,[11] using THF as solvent and Et_3N as base, we observed a significant improvement in the reactivity and selectivity when a combination of a silver salt and the DTBM-segphos ligand[12] was used as a catalyst system. Under these conditions a mixture of three pyrrolidines was observed by ^{1}H-NMR analysis of the crude mixtures. The isolation of the resulting spirocyclic intermediate **3** was not feasible because of its instability during the purification process. Thus, it was quantitatively transformed into the corresponding dimethyl-4-benzamidopyrrolidine-2,4-dicarboxylates by treatment of the reaction mixture with a solution of HCl in MeOH. Under these

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain. E-mail: javier.adrio@uam.es, juancarlos.carretero@uam.es; Fax: +34 914973966

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and NMR spectra. CCDC 924149 and 924150. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc41663a

Table 1 Optimization of the reaction conditions



Entry	X	Solvent	Base	T (°C)	t (h)	^{1}H-NMR ratio[a] 4 : 5 : 6	Yield 4 + 5[b] (%)	ee[c] (%) 4a	ee[c] (%) 5a
1	10	THF	Et_3N	rt	16	54 : 23 : 23	44	79	86 (45)[d]
2	10	CH_2Cl_2	Et_3N	rt	16	49 : 29 : 22	53	94	84
3	10	Toluene	Et_3N	rt	16	65 : 20 : 15	42	96	99
4	10	Toluene	—	rt	16	80 : 20 : 0	62	95	76
5	10	Toluene	—	−10	16	97 : 3 : 0	74	99	82
6	5	Toluene	—	−10	16	98 : 2 : 0	66	99	—
7	3	Toluene	—	−10	48	95 : 5 : 0	63	99	—
8	1	Toluene	—	−10	168	—	—	—	—

[a] Using ^{1}H-NMR from the crude reaction mixtures. [b] Yield of the **4** + **5** mixture after column chromatography. [c] Using HPLC, see ESI for details. [d] ee of **6a**.

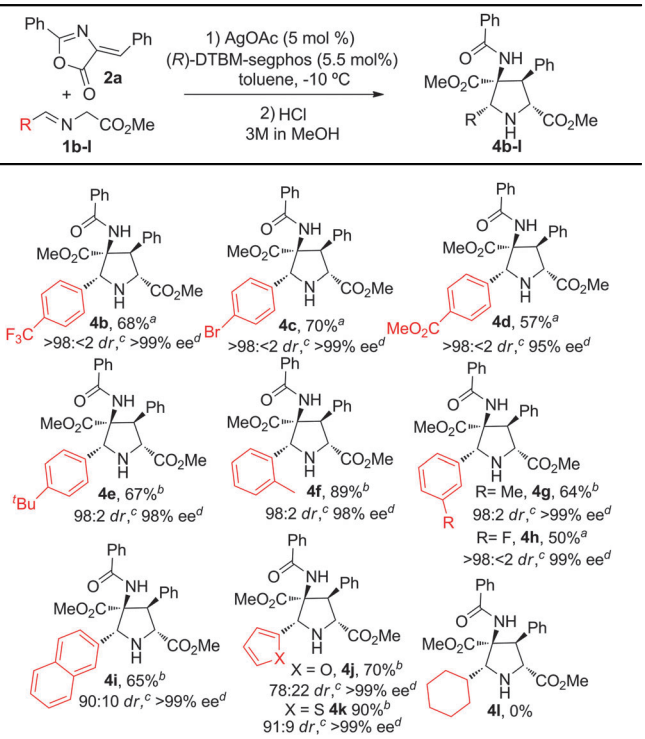
starting reaction conditions isomer **4a** was obtained in 79% ee, isomer **5a** in 86% ee and isomer **6a**[13] in 45% ee (Table 1, entry 1). Next, we endeavour to optimize the reaction conditions to improve both the diastereo- and enantioselectivity of the process. We observed an important improvement in the enantioselectivity using CH_2Cl_2 as solvent (94% ee for **4a**, entry 2) and even higher in toluene (96% ee for **4a**, entry 3).

Interestingly, it was found that in the absence of an added base the reaction takes place with a similar yield and enantioselectivity but higher diastereoselectivity (entry 4). When the reaction was carried out at −10 °C an additional enhancement in the diastereo- and enantioselectivity was observed to provide **4a** with very high diastereoselectivity (97 : 3 ratio) and excellent enantioselectivity (entry 5). The catalyst loading could be reduced to 5 mol% with similar reactivity and selectivity (entry 6). However, a much longer reaction time was needed using a 3 mol% of catalyst (entry 7) and no reaction was observed with 1 mol% (entry 8).

With these optimal reaction conditions in hand, the scope of the 1,3-dipolar cycloaddition with regard to the substitution in the azomethine ylide was investigated. As shown in Table 2 the cycloaddition tolerates a broad substitution at the aromatic ring regardless of the steric and electronic properties of the substituent. In all cases the corresponding pyrrolidines **4** were isolated with moderate to good yields, almost complete diastereoselectivity and excellent enantioselectivity (cycloadducts **4b–4i** in up to 90% yield, dr from 78 : 22 to >98 : 2, and ee from 95 to >99%). The procedure was also applied to heteroaryl substituted glycine derivatives **1j** and **1k** with excellent enantiocontrol, albeit with lower diastereocontrol. In contrast, no reaction was observed when an alkyliminoester **1l** was tested under the same reaction conditions. The stereochemical and configurational assignments of isomers **4c** and **6c** were unequivocally established by X-ray diffraction analysis.[14]

To further study the scope of this transformation, the effect of the substitution at the alkylidene azlactone partner on the reactivity and selectivity was investigated (Table 3). First, a variety

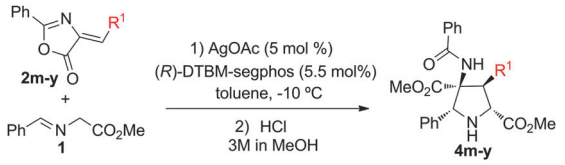
Table 2 Scope of the reaction: substitution at the azomethine ylide precursor

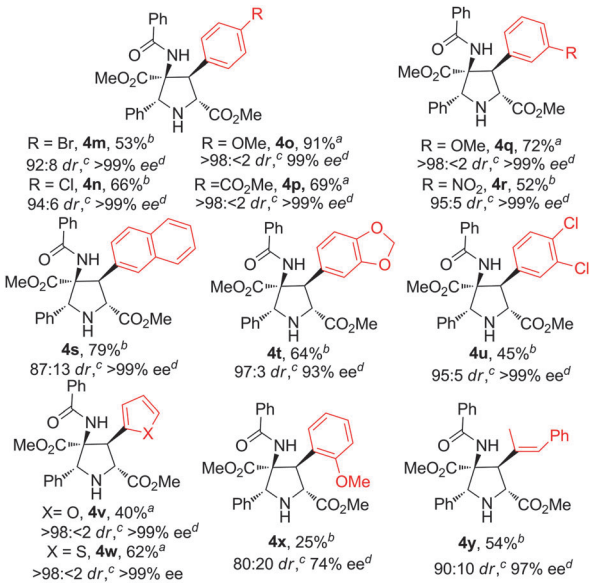


[a] Isolated yields of major diastereomer **4** after column chromatography. [b] Isolated yields of the **4** + **5** mixture after column chromatography. [c] Diastereomeric **4** : **5** ratio using ^{1}H-NMR from the crude reaction mixtures. [d] ee determined using chiral HPLC, see ESI for details.

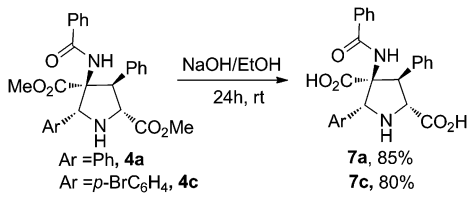
of aryl substituted azlactones were tested as dipolarophiles. Both electron donating and withdrawing substituents were well tolerated in the cycloaddition that proceeded with high diastereoselectivities providing the pure adducts **4m–4u** in 45–91% yields and excellent enantioselectivities (93 → >99% ee). The reactions also efficiently transformed azlactones with heteroaromatic substituents into the corresponding pyrrolidines (**4v** and **4w**). Only in the case of *ortho* arylsubstituted azlactones the reactivity and

Table 3 Scope of the reaction: substitution at the alkylidene azlactone





[a] Isolated yields of major diastereomer **4**. [b] Isolated yields of the **4** + **5** mixture after column chromatography. [c] Diastereomeric ratios **4**:**5** using ^{1}H-NMR from the crude mixtures. [d] ee determined using chiral HPLC, see ESI.



Scheme 2

selectivity dropped significantly (cycloadduct **4x**). Alkenyl azlactones were also suitable substrates for this reaction, providing the major isomer **4y** with excellent enantioselectivity (97% ee).

The selective hydrolysis of the ester groups of the pyrrolidines **4a** and **4c** was readily achieved in the presence of NaOH in EtOH, providing the pyrrolidine dicarboxylic acids **7a** and **7c** in 85% and 80% yield respectively, without any detectable epimerization[15] (Scheme 2).

In summary, we have developed an efficient methodology for the preparation of 4-amidopyrrolidine-2,4-dicarboxylates *via* catalytic asymmetric [3+2] cycloaddition of azomethine ylides with alkylidene azlactones. The use of Ag^I–DTBM-segphos as catalyst leads to the formation of the corresponding cycloadducts with excellent levels of diastereoselectivity and enantiocontrol (up to ≥99% ee). Hydrolysis of the ester groups under standard conditions afforded the 4-amidopyrrolidine 2,4-dicarboxylic acids which encompass potential pharmacological applications.

Financial support for this work from the Ministerio de Ciencia e Innovación of Spain (MICINN, CTQ2009-07791), the Ministerio de Economia y Competitividad (MINECO, CTQ2012-35790) and CAM (project AVANCAT; S2009/PPQ-1634) is gratefully acknowledged. M.G.-E. thanks the MICINN for a predoctoral fellowship. We thank the Takasago Company (Dr Taichiro Touge) for generous loans of segphos chiral ligands.

Notes and references

1 For selected reviews, see: (*a*) W.-F. Xu, X.-C. Cheng, Q. Wang and H. Fang, *Curr. Med. Chem.*, 2008, **15**, 374; (*b*) C. V. Calliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748.
2 (*a*) T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta and T. Fukuyama, *Org. Lett.*, 2008, **10**, 169; (*b*) S. Pizzarello, *Acc. Chem. Res.*, 2006, **39**, 231; (*c*) O. Yasufumi and S. Tetsuro, *Eur. J. Org. Chem.*, 2005, 5127.
3 For reviews, see: (*a*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*b*) *Proc. Natl. Acad. Sci., USA*, 2010, **107** special feature issue on organocatalysis.
4 (*a*) A. Pedretti, L. De Luca, C. Sciarrillo and G. Vistoli, *ChemMedChem*, 2008, **3**, 79; (*b*) M. Frauli, N. Hubert, S. Schann, N. Triballeau, H.-O. Bertrand, F. Acher, P. Neuville, J.-P. Pin and L. Prézeau, *Mol. Pharmacol.*, 2007, **71**, 704; (*c*) J. A. Monn, M. J. Valli, B. G. Johnson, C. R. Salhoff, R. A. Wright, T. Howe, A. Bond, D. Lodge, L. A. Spangle, J. W. Paschal, J. B. Campbell, K. Griffey, J. P. Tizzano and D. D. Schoepp, *J. Med. Chem.*, 1996, **39**, 2990.
5 C. E. Schafmeister, Z. Z. Brown and S. Gupta, *Acc. Chem. Res.*, 2008, **41**, 1387.
6 (*a*) M. Katoh, C. Hisa and T. Honda, *Tetrahedron Lett.*, 2007, **48**, 4691; (*b*) M. J. Valli, D. D. Schoepp, R. A. Wright, B. G. Johnson, A. E. Kingston, R. Tomlinson and J. A. Moon, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1985.
7 For recent reviews, see: (*a*) J. Adrio and J. C. Carretero, *Chem. Commun.*, 2011, **47**, 6784; (*b*) C. Nájera and J. M. Sansano, *Top. Heterocycl. Chem.*, 2008, **12**, 117.
8 For selected very recent references see: (*a*) A. D. Lim, J. A. Codelli and S. E. Reisman, *Chem. Sci.*, 2013, **4**, 650; (*b*) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2012, **51**, 9512; (*c*) M. Potowski, M. Schürmann, P. Antonchick and H. Waldmann, *Nat. Chem. Biol.*, 2012, **8**, 428.
9 (*a*) T.-L. Liu, Z.-L. He and C.-J. Wang, *Chem. Commun.*, 2011, **47**, 9600; (*b*) T.-L. Liu, Z.-L. He, Q.-H. Li, H.-Y. Tao and C.-J. Wang, *Adv. Synth. Catal.*, 2011, **353**, 1713; (*c*) T.-L. Liu, Z.-L. He, H.-Y. Tao, Y.-P. Cai and C.-J. Wang, *Chem. Commun.*, 2011, **47**, 2616; (*d*) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Scharmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735.
10 (*a*) D. Wang, Y. Wei and M. Shi, *Chem. Commun.*, 2012, **48**, 2764; (*b*) B. M. Trost and P. J. Morris, *Angew. Chem., Int. Ed.*, 2011, **50**, 4236; for diastereoselective 1,3 dipolar cycloaddition of azomethine ylides to chiral oxazolidinones, see: (*c*) S. G. Pyne, J. Safaei-G and F. Koller, *Tetrahedron Lett.*, 1995, **36**, 2511.
11 A variety of metal salts and structurally diverse chiral ligands were tested in this cycloaddition, see ESI† for details.
12 For the use of segphos ligands in catalytic asymmetric 1,3-dipolar cycloadditions of azomethine ylides, see: (*a*) Y. Yamashita, T. Imaizumi and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2011, **50**, 4893; (*b*) J. Hernández-Toribio, S. Padilla, J. Adrio and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2012, **51**, 8854; (*c*) M. González-Esguevillas, J. Adrio and J. C. Carretero, *Chem. Commun.*, 2012, **48**, 2149; (*d*) Y. Oderaotoshi, W. Cheng, S. Fujitomi, Y. Kasano, S. Minakata and M. Komatsu, *Org. Lett.*, 2003, **5**, 5043.
13 The absolute and relative configuration of isomers **4**, **5** and **6** was determined by X-ray diffraction analysis and NMR studies, see ref. 14 and ESI†.
14 CCDC 924149 (**4c**) and 924150 (**6c**).† Compound **6c** was obtained using different reaction conditions ((*R*)-Tol-Binap as a ligand), see ESI† for details. For previous examples of azomethine ylide dipolar cycloadditions where 2,5-*trans* pyrrolidine derivatives were obtained, see: (*a*) A. Awata and T. Arai, *Chem.–Eur. J.*, 2012, **18**, 8278; (*b*) E. E. Maroto, S. Filippone, A. Martín-Domenech, M. Suarez and N. Martín, *J. Am. Chem. Soc.*, 2012, **134**, 12936; (*c*) T. Arai, N. Yokoyama, A. Mishiro and H. Sato, *Angew. Chem., Int. Ed.*, 2010, **49**, 7895.
15 F. Clerici, M. L. Gelmi, A. Gambini and D. Nava, *Tetrahedron*, 2001, **57**, 6429.