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Silver-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with β-Boryl Acrylates

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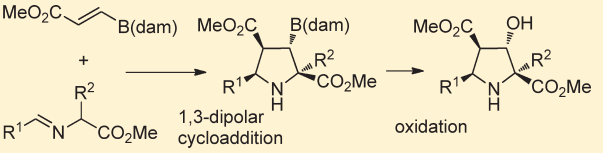
Supporting Information

ABSTRACT: The Ag-catalyzed 1,3-dipolar cycloaddition of (E)-β-borylacrylates with azomethine ylides is described. The resulting 3-borylpyrrolidine derivatives were obtained in high yields and complete endo selectivities using AgOAc/dppe as catalyst system and B(dam) as boryl group. Transformation of the B(dam) group into pinacol borane and oxidation afforded 3-hydroxyproline derivatives in high yields.



Hydroxypyrrolidines are widely present in natural products and biologically active compounds.[1] For instance, the 3-hydroxypyrrolidine scaffold is found in a variety of alkaloids with varied and potentially useful biological activities, such as salinosporamide C,[2] barnidipine,[3] retronecine,[4] preussin,[5] and detoxin A_1.[6] Furthermore, 3-hydroxyproline derivatives are present in peptides and cyclopeptides with great therapeutic potential.[7]

Because of this interest, a variety of methods have been reported for the synthesis of hydroxypyrrolidines.[8] However, there is room for improvement, especially in the context of the stereoselective synthesis of densely functionalized hydroxypyrrolidines. The 1,3-dipolar cycloaddition of azomethine ylides derived of α-iminoesters with activated alkenes constitutes a powerful and convergent tool for the preparation of substituted pyrrolidines and proline derivatives.[9] Since the pioneering reports by Grigg,[10] different catalytic systems based on the combination of a metal salt with a mild base have been developed, including a wide variety of catalytic asymmetric procedures.[11]

One of the main synthetic limitations of this strategy is that it is only applicable to low LUMO dipolarophiles, mainly electron-deficient conjugated alkenes, hampering the preparation of pyrrolidines with electron-donating oxygenated substituents at position 3 of the pyrrolidine ring. Taking into account that alkenylboron derivatives have been successfully employed as olefin partners in 1,3-dipolar cycloadditions of diazoalkanes,[12] nitrones,[13] nitrile oxides,[14] and nonstabilized azomethine ylides,[15] we envisaged that 3-borylacrylates could be suitable dipolarophiles in the metal-catalyzed 1,3-dipolar cycloaddition of α-iminoesters (Scheme 1). To the best of our knowledge only an isolated example of this strategy has been previously described.[16] Given the synthetic versatility of alkylboronates, this approach could lead to the straightforward stereoselective preparation of proline derivatives, especially 3-hydroxypyrrolidines.

Our initial studies were focused on the reaction between *N*-benzylideneglycine methyl ester (**1a**) and the activated pinacol boronate **2**[17] in the presence of a variety of copper and silver salts, (±)-Binap as ligand, and Et_3N as base in THF at room temperature (Table 1). We found the best reactivity using AgOAc as catalyst[18] (Table 1, entry 1). However, all the attempts aimed to purify the boryl-substituted pyrrolidine adduct,[19] as well as the direct oxidation of the C−B bond in the crude reaction mixture,[20] resulted in extensive decomposition.

In order to increase the stability of the 3-borylpyrrolidine adduct, the alkenylboronic acid **3** and their derivatives **4**−**6** were prepared and examined under similar reaction conditions (entries 2−5). The reaction of boronic acid **3** afforded a complex mixture of pyrrolidines,[21] while no reaction was observed from the trifluoroalkylborate salt[22] **4** or the mida boronate[23] **5**, likely due to the insolubility of these species in typical organic solvents (entries 3 and 4). More encouraging, the 1,8-diaminonaphtalene (dam) derivative[24] **6** afforded the pyrrolidine **7a** with high endo selectivity in 20% yield after standard column chromatography (entry 5). Gratifyingly, further optimization of the reaction conditions, mainly by changing the solvent and, especially, the base, allowed a dramatic increase in the efficiency of the process (entries 6−8), reaching 77% yield in pyrrolidine **7a** using LiHMDS as base in toluene (entry 8). Interestingly, after a survey of other commercially available biphosphines,[18] a complete endo selectivity and excellent yield (93%) was obtained when dppe was used as ligand (entry 9). The relative configuration of pyrrolidine *endo*-**7a** was unequivocally established by X-ray diffraction.[25]

With these optimal reaction conditions in hand, we next studied the scope of the reaction with regard to the azomethine ylide precursor (Table 2). Similar to the behavior of the model iminoester **1a**, only the endo isomer was observed in all of the examples studied. All aryl imine glycinate derivatives afforded good to excellent yields, after silica gel chromatographic purification, regardless of the electronic character of the substituents at the ortho, meta, or para position of the aromatic ring (entries 1−7). Similar results were obtained with heteroaromatic α-iminoesters (entries 8 and 9). The procedure can be also applied to

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Scheme 1. Strategy for the Stereoselective Synthesis of Substituted 3-Hydroxypyrrolidines

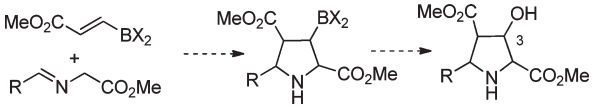
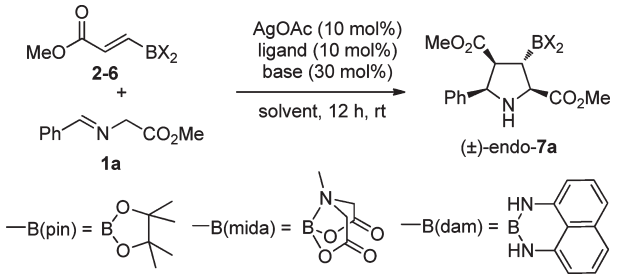


Table 1. Optimization Experiments for the Model Reaction



entry	BX_2	ligand	base	endo/exo[a]	yield[b] (%)
1[c]	B(pin) (**2**)	(±)-binap	Et_3N	>98/<2	
2[c]	$B(OH)_2$(**3**)	(±)-binap	Et_3N		
3[c]	BF_4K(**4**)	(±)-binap	Et_3N		
4[c]	B(mida) (**5**)	(±)-binap	Et_3N		
5[d]	B(dam) (**6**)	(±)-binap	Et_3N	87/13	20
6[e]	B(dam) (**6**)	(±)-binap	Et_3N	69/31	48
7[e]	B(dam) (**6**)	(±)-binap	KHMDS	66/34	58
8[e]	B(dam) (**6**)	(±)-binap	LiHMDS	88/12	77
9[e]	B(dam) (**6**)	dppe[f]	LiHMDS	>98/<2	93

[a] By ^{1}H NMR from the crude reaction mixtures. [b] Isolated yield of *endo*-**7a**. [c] THF as solvent. [d] Et_2O as solvent. [e] Toluene as solvent. [f] dppe: 1,2-bis(diphenylphosphino)ethane.

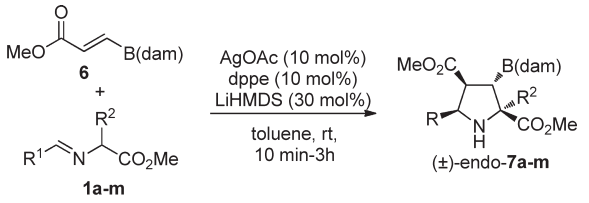
the more challenging alkyl-substituted imines, providing 5-alkylpyrrolidines **7k** and **7l** in reasonable yields (entries 10 and 11). In contrast, the alanine-based iminoester **1m** was much less reactive, affording the pyrrolidine adduct **7m**, with a quaternary center at C-2, in 27% yield (entry 12).

To highlight the synthetic interest of 3-borylpyrrolidines **7**, the oxidation to the corresponding alcohols was next explored. The best result was obtained by treatment of the N-protected Cbz derivative **8** with pinacol borane under acidic conditions, followed by direct oxidation of the resulting pinacol borane mixture using standard conditions (H_2O_2, NaOH; Scheme 2).

Finally, we explored the viability of developing a catalytic asymmetric version of this 1,3-dipolar cycloaddition. To this end, a set of commercially available chiral biphosphines were tested as ligands.[26] The P,P axially chiral DTBM-Segphos ligand[27,28] proved to be the best ligand, providing the cycloadduct **2** in 78% yield and moderate 60% ee[29] (Scheme 3). No improvement in the enantioselectivity was observed when this reaction was performed at 0 °C instead of room temperature.

In summary, 3-borylacrylates are suitable dipolarophiles in metal-catalyzed 1,3-dipolar cycloadditions of azomethine ylides. Using AgOAc/dppe as catalyst system, LiHMDS as base, and B(dam) as boryl group, good yields and complete endoselectivities were achieved in the reaction with a variety of glycinate

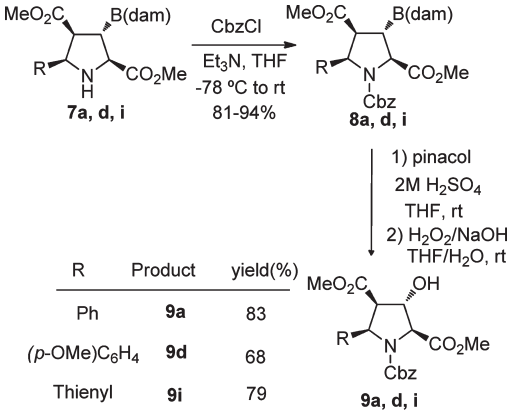
Table 2. Scope for the Azomethine Ylide Precursor



entry	R^1	R^2	product	yield[a] (%)
1	*p*-BrC_6H_4	H	**7b**	82
2	*p*-ClC_6H_4	H	**7c**	68
3	*p*-$MeOC_6H_4$	H	**7d**	64
4	*o*-MeC_6H_4	H	**7e**	95
5	*m*-MeC_6H_4	H	**7f**	83
6	*m*-FC_6H_4	H	**7g**	88
7	naphthyl	H	**7h**	67
8	thienyl	H	**7i**	98
9	furyl	H	**7j**	78
10	Cy	H	**7k**	49
11	^{t}Bu	H	**7l**	71
12	Ph	Me	**7m**	27

[a] Isolated yield of endo adduct.

Scheme 2



imines. In the presence of DTBM-Segphos as chiral ligand the model 1,3-dipolar cycloaddition took place with moderate enantioselectivity (60% ee). The oxidation of the 3-boryl substituted aducts highlights the usefulness of this method for the preparation of 3-hydroxypyrrolidines.

EXPERIMENTAL SECTION

Typical Procedure for the 1,3-Dipolar Cycloaddition: (2*S,3*S**,4*S**,5*R**)-Dimethyl 3-(2,3-Dihydro-1*H*-naphtho-[1,8-*de*]-1,3,2-diazoborinyl)-5-phenylpyrrolidine-2,4-dicarboxylate (*endo*-7a).** To a solution of dppe ligand (5.2 mg, 0.013 mmol) and AgOAc (2.0 mg, 0.013 mmol) in toluene (0.5 mL), under nitrogen atmosphere, at room temperature, were successively added a solution of methyl (*E*)-*N*-benzylideneglycinate (27 mg, 0.15 mmol) in toluene (0.5 mL) and LiHMDS (1 M in THF, 35.0 μL, 0.035 mmol). The resulting solution was added to a suspension of *trans*-methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazoborinin-2(3*H*)-yl)-acrylate (30 mg, 0.12 mmol)

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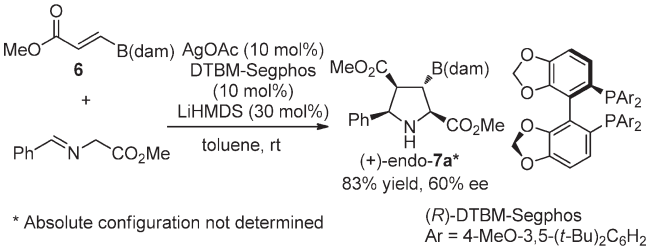
Scheme 3. Catalytic Asymmetric Version



in toluene (1.0 mL). Once the starting material was consumed (monitored by TLC), the mixture was filtered through Celite with the aid of CH_2Cl_2 (5.0 mL), and the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (hexane−EtOAc 2:1) to afford the cycloadduct **7a** (48 mg, 93%, white solid): mp 209−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H), 7.13−7.08 (m, 2H), 7.04−7.01 (m, 2H), 6.35−6.33 (m, 2H), 6.10 (bs, 2H), 4.66 (d, J = 8.8 Hz, 1H), 4.04 (d, J = 10.6 Hz, 1H), 3.85 (s, 3H), 3.43 (dd, J = 10.6, 8.8 Hz, 1H), 3.27 (s, 3H), 3.11 (bs, 1H), 2.33 (t, J = 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 172.8, 140.6, 139.9, 136.2, 128.3, 127.9, 127.5, 127.1, 119.8, 117.8, 106.0, 65.2, 63.0, 54.1, 52.7, 51.6 (the boron-bound carbon was not detected due to quadrupolar relaxation); HRMS (FAB+) calcd for $C_{24}H_{24}BN_3O_4$ $[M]^+$ 429.1860, found 429.1866.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray crystallographic data of compound *endo*-**7a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) See the Supporting Information for catalyst optimization studies.

(19) Silica gel, Et_3N deactivated silica gel, alumina flash chromatography, and recrystallization in several solvents were tested.

(20) $NaBO_4$, NMO, and H_2O_2 were tested as oxidizing agents.
(21) The undesired dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate resulting from a deprotoborylation process was detected in the reaction mixture.
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(25) See the Supporting Information for details on the X-ray structure of *endo*-**7a**.
(26) See the Supporting Information for details.
(27) For a review on biaryl-type biphosphine ligands, see: Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405–5432.
(28) For the use of AgOAc/KHMDS/DTBM-Segphos as catalyst system in the asymmetric 1,3-dipolar cycloaddition of α-aminophosphonate Shiff bases, see ref 11m.
(29) Determined by HPLC; see the Supporting Information for details.