ChemComm

Chemical Communications

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Volume 49 | Number 63 | 14 August 2013 | Pages 7015–7096

ISSN 1359-7345

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1359-7345(2013)49:63;1-W

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Unusual *anti*-selective asymmetric conjugate addition of aldehydes to nitroalkenes catalyzed by a biphenyl-based chiral secondary amine†

Cite this: *Chem. Commun.*, 2013, **49**, 7028

Received 6th April 2013,
Accepted 25th April 2013

DOI: 10.1039/c3cc42488j

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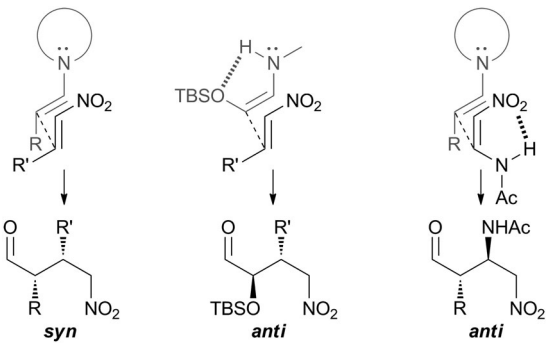
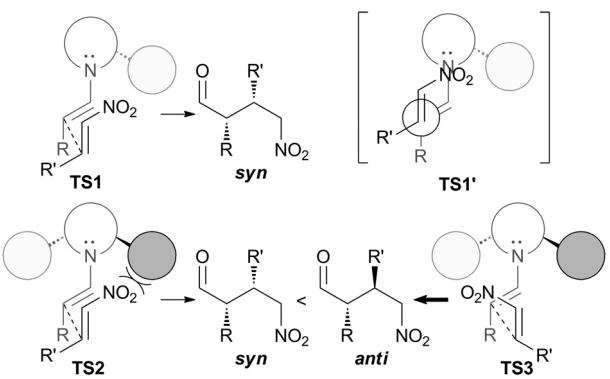
Unusual *anti*-selectivity was observed in the conjugate addition of aldehydes to nitroalkenes, when a biphenyl-based chiral secondary amine was used as catalyst.

The catalytic asymmetric conjugate addition of carbon nucleophiles to electron-deficient olefins is one of the most fundamental and reliable C–C bond forming reactions in synthetic organic chemistry.[1] In the area of organocatalysis, a large number of asymmetric conjugate addition reactions have been developed to date.[2,3] Consequently, a wide variety of electron-deficient olefins are now applicable as acceptors to the amine-catalyzed conjugate additions through an enamine intermediate.[3] Among a number of electron-deficient olefins, nitroalkenes are most frequently used in the chiral secondary amine-catalyzed reactions of aldehydes,[4–6] giving *syn*-adducts as major diastereomers through the *E*-enamine intermediate (Scheme 1, left).[4a,5b,7] On the other hand, Barbas and co-workers have realized the first *anti*-selective conjugate addition to nitroalkenes through generation of the *Z*-enamine by a combination of a primary amine catalyst and a siloxyacetaldehyde (Scheme 1, middle).[6l] Ma and co-workers have also reported the unusual *anti*-selective conjugate addition to the specific *Z*-nitroalkene (Scheme 1, right).[6p] However, the development of *anti*-selective conjugate addition between standard *E*-nitroalkenes and simple aldehydes is still challenging,[8,9] since simple aldehydes tend to form the corresponding *E*-enamines and thus led to the *syn*-adducts. Herein, we wish to report a rare example of *anti*-selective asymmetric conjugate addition to nitroalkenes catalyzed by axially chiral secondary amines.

In the most amine-catalyzed conjugate addition, the unsymmetrical secondary amines (*e.g.* proline derivatives) were used as catalysts. The high *syn*-selectivity observed can be explained by the acyclic synclinal transition state model **TS1′** (Scheme 2).[4a,5b] While the geometry of the enamine intermediate can be controlled by the catalyst, the mode of the nitroalkene approach is less susceptible to the steric environment



Scheme 1 General *syn*-selective conjugate addition (left) and unusual *anti*-selective conjugate additions by Barbas (middle) and Ma (right).



Scheme 2 Strategy for *anti*-selective conjugate addition.

created by the catalyst. On the other hand, a C_2-symmetric secondary amine catalyst having bulky substituents seems to slow down or inhibit the *syn*-selective reaction through a similar transition state **TS2** due to the severe steric repulsion between one of the bulky substituents of the catalyst and the nitro group of nitroalkenes. Consequently, the relative rate of the reaction through **TS3** which gives the *anti*-adduct might be increased.[7]

To verify our hypothesis, we prepared a biphenyl-based chiral secondary amine (*S*)-**1** with phenyl groups at 3,3′-positions, and the reaction of propanal with β-nitrostyrene in the presence of 10 mol%

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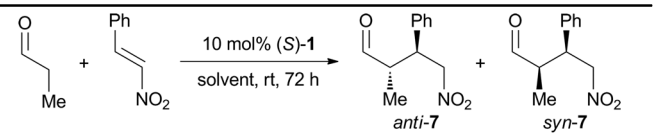
† Electronic supplementary information (ESI) available: See DOI: 10.1039/c3cc42488j

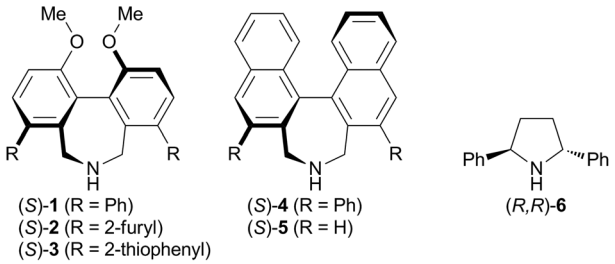
Table 1 Conjugate addition of propanal to nitrostyrene catalyzed by (*S*)-**1**[a]



Entry	Solvent	Yield[b] (%)	*anti*/*syn*[c]	ee (*anti*/*syn*)[d] (%)
1	Cyclohexane	76	1/1.6	90/91
2	Toluene	61	1/1.0	90/86
3	$CHCl_3$	89	1/1.6	82/83
4	THF	40	1.2/1	92/81
5	Dioxane	28	1.8/1	91/74
6	DME	51	1.6/1	93/79
7	MeCN	99	1/1.1	95/89
8	DMF	70	1/1.0	93/59
9	HMPA	90	1/3.2	65/21
10	DMSO	35	2.3/1	95/57
11	Sulfolane	99	1.1/1	96/88
12	MeOH	10	1/1.0	96/86
13	H_2O	99	1/1.4	93/91
14	Neat	43	1/1.8	93/91

[a] The reaction of propanal (1.0 mmol) with nitrostyrene (0.1 mmol) was carried out in the presence of (*S*)-**1** (0.01 mmol) in a solvent (0.2 mL). [b] Isolated yield. [c] Determined using ^{1}H-NMR. [d] Determined by HPLC using a chiral column.

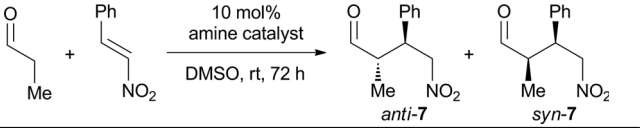
of (*S*)-**1** was examined in various solvents (Table 1). In most cases tested, a substantial amount of *anti*-adduct **7** was obtained in high enantioselectivity. Fortunately, *anti*-adduct **7** was slightly predominant in ethereal solvents or DMSO, albeit long reaction times were required (entries 4–6 and 10).



We then investigated the conjugate addition of propanal to β-nitrostyrene in DMSO in the presence of various biaryl-based chiral secondary amine catalysts (Table 2).[10] Among catalysts tested, (*S*)-**3** having thiophenyl groups showed slightly higher *anti*-selectivity compared to (*S*)-**1** having phenyl groups (entry 3). Substituents at 3,3′-positions were found to be crucial to obtain *anti*-selectivity and high enantioselectivity (entry 4 *vs.* 5). Use of the C_2-symmetric 2,5-diphenylpyrrolidine (*R*,*R*)-**6** resulted in no conversion (entry 6). It is noteworthy that the *anti*-selectivity as well as the yield can be improved by addition of the appropriate amount of H_2O (1–3 equiv.) (entries 7 and 8).[11]

In the presence of 10 mol% of (*S*)-**3**, the direct asymmetric conjugate addition to several other nitroalkenes was examined (Table 3). In general, these direct asymmetric conjugate additions gave the corresponding *anti*-adducts as major diastereomers with good to excellent enantioselectivity. When butanal was used instead of propanal as a nucleophile, a decrease in stereoselectivities was observed (entry 10). A sterically hindered aldehyde, 3-methylbutanal, provided no product (entry 11).

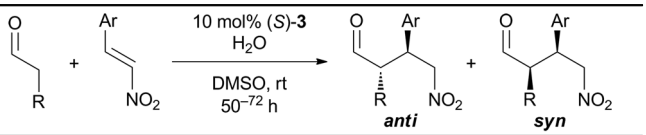
Table 2 Conjugate addition of propanal to nitrostyrene catalyzed by biaryl-based amine catalysts[a]



Entry	Catalyst	Yield[b] (%)	*anti*/*syn*[c]	ee (*anti*/*syn*)[d] (%)
1	(*S*)-**1**	35	2.3/1	95/57
2	(*S*)-**2**	44	2.4/1	93/38
3	(*S*)-**3**	38	2.7/1	95/58
4	(*S*)-**4**	32	1.9/1	94/68
5	(*S*)-**5**	23	1/2.7	34/38
6	(*R*,*R*)-**6**	n.d.	—	—
7[e]	(*S*)-**3**	83	3.3/1	96/64
8[f]	(*S*)-**3**	81	2.9/1	96/67
9[g]	(*S*)-**3**	82	2.7/1	96/73

[a] The reaction of propanal (1.0 mmol) with nitrostyrene (0.1 mmol) was carried out in the presence of a catalyst (0.01 mmol) in DMSO (0.2 mL). [b] Isolated yield. [c] Determined using ^{1}H-NMR. [d] Determined by HPLC using a chiral column. [e] H_2O (1 equiv.). [f] H_2O (3 equiv.). [g] H_2O (10 equiv.).

Table 3 Conjugate addition to various nitrostyrenes catalyzed by (*S*)-**3**[a]



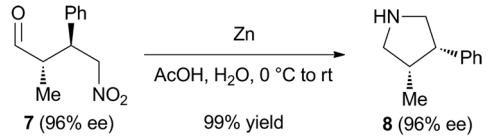
Entry	R, Ar	Yield[b] (%)	*anti*/*syn*[c]	ee (*anti*/*syn*)[d] (%)
1	Me, Ph	83	3.3/1	96/64
2	Me, 4-Me-C_6H_4	86	4.1/1	96/46
3	Me, 4-MeO-C_6H_4	88	2.8/1	93/45
4	Me, 4-Br-C_6H_4	73	3.9/1	97/73
5	Me, 4-F-C_6H_4	95	3.3/1	96/72
6	Me, 3-F-C_6H_4	95	2.5/1	91/75
7	Me, 2-F-C_6H_4	99	2.4/1	99/77
8	Me, 3-furanyl	93	3.2/1	86/39
9	Me, 2-thiophenyl	84	3.1/1	86/63
10[e]	Et, Ph	85	1.4/1	91/38
11	i-Pr, Ph	n.r.	—	—

[a] The reaction of propanal (1.0 mmol) with nitrostyrene (0.1 mmol) was carried out in the presence of (*S*)-**3** (0.01 mmol) and H_2O (0.1 mmol) in DMSO (0.2 mL). [b] Isolated yield. [c] Determined using ^{1}H-NMR. [d] Determined by HPLC using a chiral column. [e] Use of 20 mol% of (*S*)-**3**.

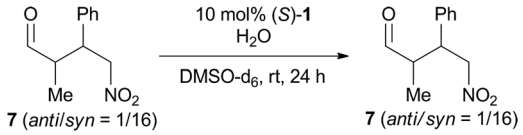
The obtained conjugate adduct was a versatile intermediate in organic synthesis and readily converted to an important chiral building block.[12] The optically enriched conjugate adduct **7** (*anti*–*syn* = 3.3/1) could be converted to pyrrolidine **8** (*cis*–*trans* = 3.0/1) without racemization by reduction of the nitro group and the subsequent reductive amination (Scheme 3).[6p]

To understand the origin of *anti*-selectivity observed in the present conjugate addition, the NMR study was conducted. When a diastereomixture of conjugate adduct **7** (*anti*–*syn* = 1/16) was treated with (*S*)-**1** under the reaction conditions, no change in the diastereomeric ratio was observed as shown in Scheme 4. This result indicated that the *anti*-selectivity in the present reaction would originate from the C–C bond forming step, not from isomerization between *anti*-adduct and *syn*-adduct under the reaction conditions.

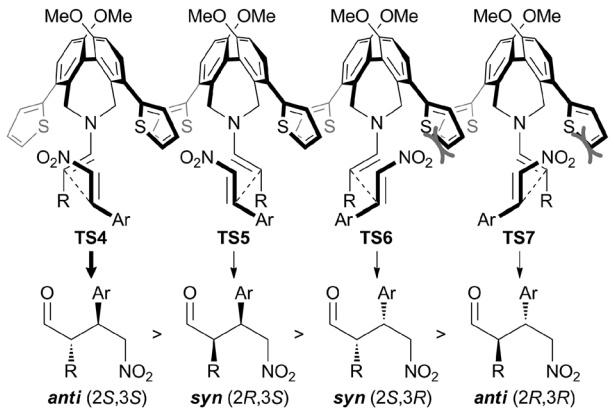
Based on the observed stereochemistry, transition state models can be proposed as shown in Scheme 5.[7] In both transition states **TS4** and **TS5**, which give major enantiomers of



Scheme 3 Transformation to pyrrolidine **8**.



Scheme 4 Attempted isomerization of **7** under the reaction conditions.



Scheme 5 Plausible transition state models.

the *anti*-adduct and the *syn*-adduct, the Si face of nitroalkene approaches the enamine intermediate. In the transition state **TS4**, the steric repulsion between nitroalkenes and the thiophenyl group of the catalyst in the same face seems not to be significant compared to that in **TS5**. On the other hand, the transition states **TS6** and **TS7** might suffer from the severe steric repulsion, leading to high enantioselectivity. Moderate enantioselectivity of *syn*-adducts might be attributed to the relatively small energy difference between **TS5** and **TS6**.

In summary, we have developed the *anti*-selective asymmetric conjugate addition of aldehydes to nitroalkenes catalyzed by the biphenyl-based chiral secondary amine (*S*)-**3**. In the present conjugate addition, hitherto less accessible *anti*-adducts could be obtained as major diastereomers in good to excellent enantioselectivity. We propose that the unusual *anti*-selectivity observed is an outcome of energy differences in modes of the nitroalkene approach in the unique steric environment created by the catalyst. While further studies to expand the substrate scope and improve the *anti*-selectivity are necessary, the conceptual validity of the catalyst design for achieving the unusual *anti*-selective conjugate addition was demonstrated.

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