Asymmetric Catalysis

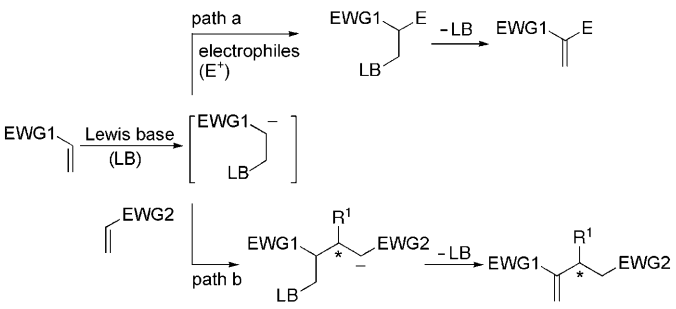
DOI: 10.1002/anie.200805558

Enantioselective Intermolecular Crossed-Conjugate Additions between Nitroalkenes and α,β-Enals through a Dual Activation Strategy**

*Cheng Zhong, Yunfeng Chen, Jeffrey L. Petersen, Novruz G. Akhmedov, and Xiaodong Shi**

The electron withdrawing group (EWG) activated alkene is considered one of the most important building blocks in organic synthesis. Its primary reaction mode is the conjugate 1,4-addition (Michael addition).[1] Recent developments within organocatalysis have led to the recognition of the enantioselective conjugate addition as one of the most important approaches to asymmetric C–C bond formation.[2] The general strategy involves carbonyl activation via iminium intermediates.[3] Moreover, such iminium catalysis has been incorporated into cascade (or domino) reactions, successful examples of which have been achieved by different research groups.[4]

Another important reaction of EWG-activated alkenes is the Lewis base (LB) promoted carbanionic nucleophilic addition (Scheme 1; path a), which produces cross-coupling



Scheme 1. Reaction pathways for electron withdrawing group activated alkenes.

products (such as the Baylis–Hillman reaction).[5] Although excellent results regarding enantioselective LB-promoted reactions have been reported by various research groups, effective LB-promoted enantioselective transformations is still considered a significant challenge.[6]

Our interest in developing Lewis base mediated stereoselective cascade reactions led to the investigation of an intermolecular crossed-conjugate addition (Scheme 1, path b). This process will produce highly functionalized products which can be additionally transformed into various structurally attractive skeletons with high atom efficiency.[7] However, there are significant challenges associated with this transformation: a) the sequential addition of the LB catalyst in the presence of two different Michael receptors (the kinetically preferred homo-crossed addition versus the desired hetero-crossed addition) and b) the stereochemical control. For these reasons, to our best knowledge, no enantioselective intermolecular crossed-conjugate addition has been reported.[8]

To study this transformation, our group investigated the double Michael addition of nitroalkenes and enones. With a β-alkyl group on the nitroalkene, the crossed-conjugate addition was successfully achieved through an irreversible β-hydride elimination (Scheme 2 A). Notably, mechanistic studies revealed that the secondary amine served as the LB catalyst and added in a 1,4 fashion to the nitroalkene, activating it for addition to the carbonyl group; L-proline did not activate the enone in this case.[7] As an attractive new C–C bond-formation method, the enantioselective transformation is highly desired. Herein, we report a dual activation approach, Lewis base/iminium, for the enantioselective nitroalkene/enal cross-coupling and its application in the synthesis of substituted pyrrolidines.

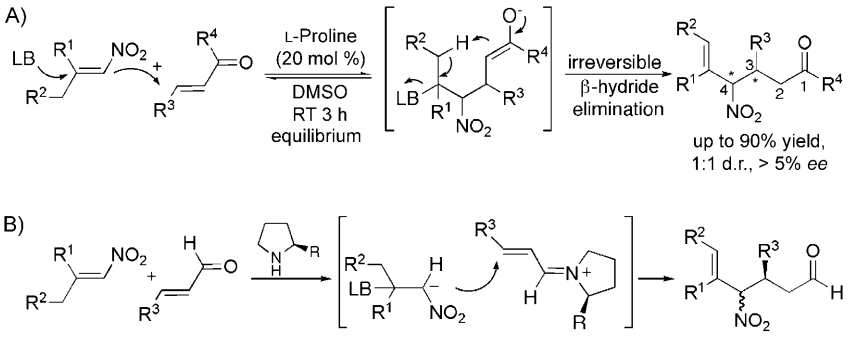
The crossed-conjugate addition shown in Scheme 2 A gave a low d.r. value because of the epimerization of the C4 stereogenic center. Thus, we rationalized that setting the C3 stereogenic center through an asymmetric Michael addition was a reasonable approach to achieving enantioselectivity (Scheme 2 B). Nitroalkene **1a** and enal **2a** were used with different chiral secondary amine catalysts to investigate the enantioselectivity of the reaction, and the results are summarized in Table 1.

Conducting the reaction in DMSO gave **3a** in modest yield with poor stereoselectivity, as there was competing polymerization of the starting materials (Table 1, entry 1). By using MeOH as the solvent, **3a** was obtained in 11% *ee* (Table 1, entry 2), which strongly supported the proposed of a dual activation mechanism (LB activation of the nitroalkene and carbonyl activation via an iminium). The use of cat-**2** at lower temperatures gave an improved enantioselectivity (Table 1, entries 3 and 6); however, the additional lowering of the reaction temperature caused a significant decrease in the reaction rate (Table 1, entry 7). This result may have been

[*] C. Zhong, Dr. Y. Chen, Prof. J. L. Petersen, Dr. N. G. Akhmedov, Prof. X. Shi
C. Eugene Bennett Department of Chemistry
West Virginia University, Morgantown, WV 26506 (USA)
Fax: (+1) 304-293-4904
E-mail: xiaodong.shi@mail.wvu.edu

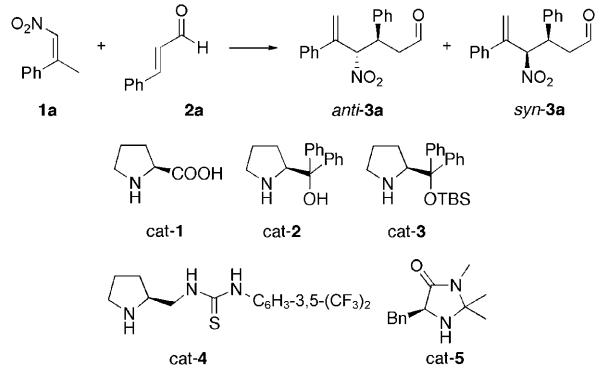
[**] We thank the C. Eugene Bennett Department of Chemistry, the Eberly College of Arts and Science, the WV Nano Initiative at West Virginia University, and the ACS-PRF for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200805558.



Scheme 2. A) Intermolecular crossed-conjugate addition and β-hydride elimination. B) Proposed dual activation method for the enantioselective crossed-Michael addition.

Table 1: Optimization of reaction conditions.[a]



Entry	Solvent	Catalyst	Co-catalyst[a]	T [°C]	t [h]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	DMSO	cat-**1**	–	RT	3	95	58	0
2	MeOH	cat-**1**	–	RT	3	86	71	11
3	MeOH	cat-**1**	–	0	12	69	64	23
4	MeOH	cat-**1**	$(MeO)_3P$	0	8	83	78	28
5	MeOH	cat-**2**	–	RT	3	57	51	35
6	MeOH	cat-**2**	–	0	12	54	47	79
7	MeOH	cat-**2**	–	−20	48	14	12	n.d.
8	MeOH	cat-**2**	$(MeO)_3P$	−20	48	69	64	90
9	MeOH	cat-**2**	$(MeO)_3P$, AcOH	−25	48	>95	90[e]	93
10	other solvents[f]	cat-**2**	–	RT	8	<55	<50	<30
11	MeOH	cat-**1**	other LBs[f]	0	24	<80	<74	<28
12	MeOH	cat-**3**	$(MeO)_3P$, AcOH	0	24	80	76	70
13	MeOH	cat-**4**	$(MeO)_3P$, AcOH	0	24	32	23	46
14	MeOH	cat-**5**	$(MeO)_3P$, AcOH	0	24	74	68	68

[a] Reaction conditions: **1a**/**2a** 1:2, concentration of **1** is 0.2 M, catalyst was 20 mol %, LB and AcOH co-catalysts were 1 equiv. [b] Based on the consumption of **1** as determined by NMR spectroscopy. [c] Yield determined by NMR analysis with 1,3,5-trimethoxybenzene as internal standard. [d] The diastereomers were separated and the *ee* values were determined by using HPLC on a chiral stationary phase (*anti* isomer only). The low d.r. (less than 2:1) in all cases favors the *anti* isomer. [e] Yield of isolated product. [f] See details in the Supporting Information. n.d. = not determined.

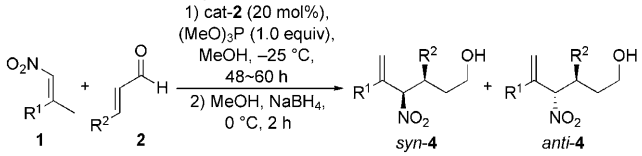
caused by the slow release of the amine catalyst from the nitroalkene addition, thereby resulting in the lack of iminium formation at low temperature. To help the release of the amine, other LBs were used as co-catalysts, and $P(OMe)_3$ was identified as the best. As expected, both the reaction rate and the enantioselectivity increased (Table 1, entry 8), and the addition of 1.0 equivalent of AcOH promoted the iminium formation, leading to **3a** in excellent yield and enantioselectivity (Table 1, entry 9). The reaction substrate scope was investigated as shown in Table 2.

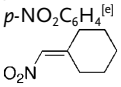
As shown in Table 2, the aldehydes **3** were reduced to alcohols **4** so that the two diastereomers could be isolated. This transformation tolerated a large range of substrates, giving good yield and good to excellent enantioselectivity.[9] Various β-substituted enals, including aryl, alkyl, and heterocyclic substituents, were all suitable for this transformation. Although the α-methyl enal gave good yields (>90%), it suffered from low stereoselectivity (<20% *ee*), which was probably caused by the poor spatial arrangement of the groups on the iminium intermediates. Both alkyl/aryl- and dialkyl-substituted nitroalkenes could be promoted in this transformation. Although monoalkyl-substituted nitroalkenes are suitable for the β-hydride elimination, they gave low yields because of significant polymerization.

To achieve high atom efficiency, it would be ideal to convert both diastereomers into one stereoisomer. It was reported that the stereogenic center to which the nitro group is appended can be removed by using transformations such as the Nef reaction, allylic nitro arrangement, and reduction.[7] To extend the scope of this new method, a simple reductive cyclization approach was developed, using the NO_2 group as the nitrogen source (Scheme 3).

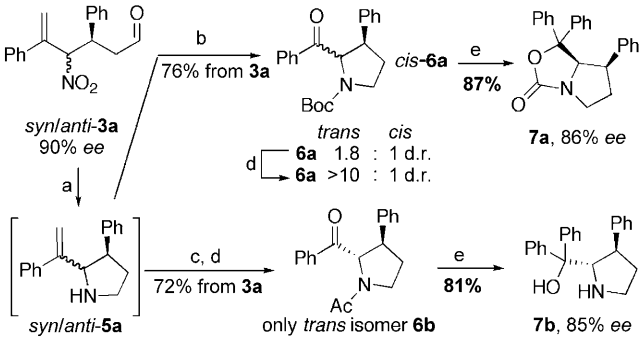
The reduction of *syn*/*anti*-**3a** gave pyrrolidines **5a**, which can be converted into carbamate- or amide-protected compounds **6a** and **6b**, respectiviely, through amine protection and ozonolysis. Mixtures of diastereomers were obtained for both **6a** and **6b** with a d.r. value less than 2:1. However, upon treatment with K_2CO_3 in MeOH, the *cis* isomer was successfully converted into the *trans* isomer, with a d.r. value greater than 10:1 for **6a**, and only the *trans* isomer was observed for **6b**. The *trans*-**6b** was then converted into **7b** with excellent yield and retention of configuration. Interestingly, treating the carbamate *cis*-**6a** with PhMgBr gave the *cis* cyclocarbamate, which significantly extends the scope of the application of this transformation; with the different protecting groups, both *cis*- and *trans*-substituted pyrrolidine can be achieved with excellent reten-

Table 2: Substrate scope of crossed-Michael addition.[a]



R^1	R^2	4[a]	Yield [%][b]	d.r.[c] (*syn*/*anti*)	*ee* [%][d]	
					syn	*anti*
Ph	Ph	**4a**	91	1:1.2	91	93
Ph	*n*Bu	**4b**	83	1:1.1	94	86
Ph	furyl	**4c**	76	1:1.1	87	87
Ph	*p*-$MeOC_6H_4$	**4d**	80	1:1.2	94	95
Ph	*p*-$NO_2C_6H_4$	**4e**	89	1:1	82	83
Ph	*o*-$NO_2C_6H_4$	**4f**	85	1:1	86	86
Ph	Me	**4g**	93	1:1.2	88	88
p-ClC_6H_4	Ph	**4h**	89	1:1.2	88	90
p-ClC_6H_4	furyl	**4i**	78	1:1.1	86	86
p-ClC_6H_4	*p*-$MeOC_6H_4$	**4j**	74	1:1.2	84	88
furyl	Me	**4k**	64	1:1	90	88
p-MeC_6H_4	Ph	**4l**	82	1:1.1	91	92
naphthyl	*p*-$NO_2C_6H_4$	**4m**	82	1:1.3	90	88
p-CNC_6H_4[e]	Ph	**4n**	86	1:1	82	80
p-$NO_2C_6H_4$[e]	Ph	**4o**	79	1:1	77	81
	Ph	**4p**	75	1:2	70	75
	p-$MeOC_6H_4$	**4q**	71	1:2.5	87	87

[a] Reaction conditions: **1**/**2** 1:3, concentration of **1** was 0.2 M. [b] Yield of isolated products. [c] The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The *ee* values were determined by HPLC on a chiral stationary phase. [e] Yields of aldehydes, no further reduction.



Scheme 3. Enantioselective synthesis of substituted pyrrolidines. a) 1. Zn/HCl, *i*PrOH; 2. $NaCNBH_3$, MeOH; b) 1. Boc_2O, Et_3N, DMAP; 2. O_3, CH_2Cl_2, −78°C; c) 1. Ac_2O, Et_3N, DMAP; 2. O_3, CH_2Cl_2, −78°C; d) K_2CO_3, MeOH; e) 1. PhMgBr, THF, 0°C; 2. NH_4Cl. Boc = *tert*-butoxycarbonyl; DMAP = *N*,*N*-dimethylaminopyridine.

tion of configuration.[9] This transformation provided a feasible approach for the preparation of substituted pyrrolidines, which are important building blocks with attractive chemical and biological activities.

In conclusion, the enantioselective crossed-conjugate addition of nitroalkene and enals was successfully developed. The wide substrate scope, excellent yields, enantioselectivity, and unique activation approach provides great potential for this new C–C bond-formation strategy. Simple transformations converted the mixture of diastereoisomeric products into a single pyrrolidine stereoisomer, thereby extending the potential application of this highly enantioselective method. The application of **7b** and its derivatives as new amine catalysts in asymmetric synthesis[10] is currently under investigation and will be reported in due course.

Experimental Section

4a: Cinnamaldehyde (396 mg, 3.0 mmol) was added to α-methyl-β-nitrostyrene (163 mg, 1.0 mmol) in MeOH (5 mL). The mixture was cooled down to −25 °C. (*S*)-(−)-2-(Diphenylhydroxymethyl)pyrrolidine (45 mg, 0.2 mmol), AcOH (60 mg, 1.0 mmol), and $(MeO)_3P$ (124 mg, 1.0 mmol) were added and the reaction mixture was stirred for 48–60 h. The resulting reaction mixture was diluted with CH_2Cl_2 (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (aq) and brine, then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue. Flash column chromatography was used to remove the excess aldehyde and other impurities. The crude products obtained were then dissolved in MeOH (20 mL), to which $NaBH_4$ (45 mg, 1.2 mmol) was added at 0 °C and monitored by TLC analysis. After the solvent had been removed, the residue was diluted with ethyl acetate (30 mL) and washed with water. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were then washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purification using flash silica gel chromatography (hexane/EtOAc 7:1) gave two alcohol diastereomers *syn*-**4a** and *anti*-**4a** each as colorless oils (270 mg, overall yield: 91 %).

For explicit experimental data, including spectroscopic data, see the Supporting Information.

Received: November 14, 2008
Published online: January 2, 2009

Keywords: asymmetric catalysis · enantioselectivity · Lewis bases · pyrrolidines

[1] For recent reviews, see: a) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065–2092; b) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147–1168; c) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.

[2] For recent reviews, see: a) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; b) K. N. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*, 487–487; c) Y. Hayashi, *J. Syn. Org. Chem. Jpn.* **2005**, *63*, 464–477.

[3] For review of iminium catalysis, see: a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87; b) S. Brandau, A. Landa, J. Franzen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411–4415; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309; c) W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580–591.

[4] Recent review, see: a) D. Enders, C. Grondal, M. R. M. Huttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581. Selected examples, see: b) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119–1122; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101–1104; c) D. Enders, M. R. M. Huttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; d) J. Wang, H. X. Xie, H. Li, L. S. Zu, W. Wang, *Angew. Chem.* **2008**, *120*, 4245–4247; *Angew. Chem. Int. Ed.* **2008**, *47*, 4177–4179.

[5] D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581 – 1588.
[6] Some recent examples, see: a) S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584 – 1663; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560 – 1638; b) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988 – 10989; c) S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176 – 6177; d) G. S. Creech, O. Kwon, *Org. Lett.* **2008**, *10*, 429 – 432; e) H. F. Duan, X. H. Sun, W. Y. Liao, J. L. Petersen, X. D. Shi, *Org. Lett.* **2008**, *10*, 4113 – 4116.
[7] X. H. Sun, S. Sengupta, J. L. Petersen, H. Wang, J. P. Lewis, X. D. Shi, *Org. Lett.* **2007**, *9*, 4495 – 4498.
[8] Intramolecular examples, see: a) V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12928 – 12929; b) L. C. Wang, A. L. Luis, K. Agaplou, H. Y. Jang, M. J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 2402 – 2403. Intermolecular example, see: c) M. Dadwal, R. Mohan, D. Panda, S. M. Mobin, I. N. N. Namboothiri, *Chem. Commun.* **2006**, 338 – 340.
[9] The stereochemistry of the products was assigned based on the X-ray crystal structures of **4e** and **6a**. CCDC 704977 (*cis*-**4e**), 704978 (*trans*-**4e**), 704979 (**6a**), and 704980 (*trans*-**6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..
[10] For recent examples, see: a) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 9362 – 9365; *Angew. Chem. Int. Ed.* **2007**, *46*, 9202 – 9205; b) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800 – 4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722 – 4724.

