CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201202660

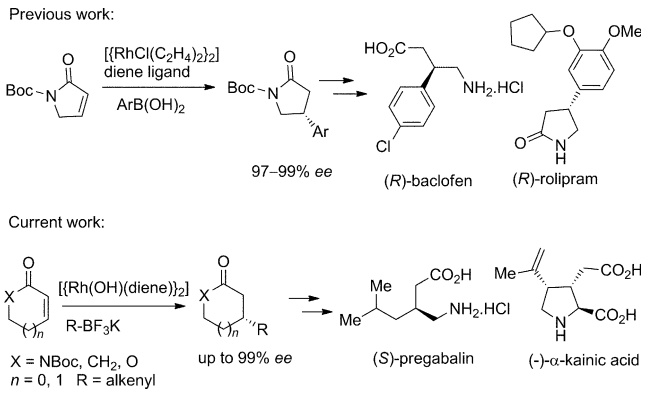
Highly Enantioselective Alkenylation of Cyclic α,β-Unsaturated Carbonyl Compounds as Catalyzed by a Rhodium–Diene Complex: Application to the Synthesis of (*S*)-Pregabalin and (−)-α-Kainic Acid

Hong-Jie Yu, Cheng Shao, Zhe Cui, Chen-Guo Feng,* and Guo-Qiang Lin*[a]

Rhodium-catalyzed asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a powerful tool to construct stereogenic carbon centers.[1] Among the organometallic reagents used in this transformation, organoboron reagents are the most popular because of their suitable reactivity, easy accessibility, low toxicity, and high stability toward air and water.[2] Since the appearance of the seminal report of Miyaura, Hayashi, and co-workers, both aryl- and alkenylboron species have been recognized as valuable coupling reagents for rhodium-catalyzed conjugate-addition reactions.[3] However, compared to arylboron reagents, which are the subject of intensive research and have many applications, the use of alkenylboron reagents is much less explored in this field, with most examples featuring only simple α,β-unsaturated ketones as reaction substrates.[4] Conjugate-addition reactions involving less reactive α,β-unsaturated esters and amides tends to be more difficult, and as such, has not been reported often. To the best of our knowledge, only the research group of Fürstner has reported on the conjugate addition of alkenylboronates to [5*H*]-furan-2-one; using a range of alkenylboronates, yields in the range of 17–65% and *ee* values as high as 82% were observed in studies toward the total synthesis of the ecklonialactones and hybridalactone.[5] The conjugate addition of alkenylboron reagents to α,β-unsaturated amides remains unexplored. Obviously, the versatility of alkenes in synthetic chemistry makes the conjugate-addition reaction of alkenylboron reagents to a wider range of Michael acceptors in high yields and high levels of enantioselectivity an attractive research target.[6,7]

The lack of research on the use of alkenylboron reagents may be partially attributed to the low stability of alkenylboronic acids compared with that of arylboronic acids. The development of more stable potassium trifluoroborates seems to be a good solution to this problem.[8] Darses, Genet, and Pucheault found that potassium alkenyltrifluoroborates can be successfully used in the rhodium-catalyzed conjugate addition to cyclic enones with high yields and high levels of enantioselectivity.[9] On the other hand, the superior performance of chiral diene ligands in rhodium-catalyzed conjugate-addition reactions may offer new opportunities for highly efficient and stereoselective alkenylation reactions for various Michael acceptors.[10]

Recently, our group reported an efficient rhodium-catalyzed reaction using arylboronic acids to prepare chiral 4-aryl lactams (Scheme 1).[11] Attempts to introduce alkenyl



Scheme 1. Rhodium–diene-catalyzed asymmetric conjugate-addition reactions. Boc = *tert*-butoxycarbonyl.

groups using the corresponding alkenylboronic acids were unsuccessful; low levels of enantioselectivity and low yields were obtained under the reaction conditions that were optimized for arylboronic acids. As part of our continuing efforts in the development of methods for the synthesis of chiral γ lactams and the development of new asymmetric rhodium-catalyzed reactions, we herein report a highly enantioselective conjugate-addition of potassium alkenyltrifluoroborates to cyclic α,β-unsaturated carbonyl compounds, and the successful application of this method to the synthesis of (*S*)-pregabalin and (−)-α-kainic acid.

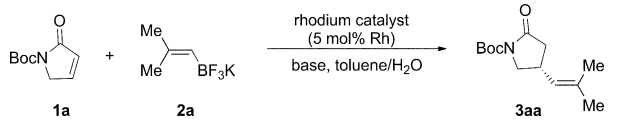
At the outset, using reaction conditions from the literature,[4g] we screened a variety of chiral ligands in the conjugate-addition reaction of trifluoroborate **2a** and lactam **1a**; the rhodium catalysts were generated in situ from the reaction of $[\{RhCl(C_2H_4)_2\}_2]$ and chiral ligands. When the phos-

[a] H.-J. Yu, C. Shao, Z. Cui, Dr. C.-G. Feng, Prof. G.-Q. Lin
Key Laboratory of Synthetic Chemistry of Natural Substances
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P. R. China)
Fax: (+86) 21-6416-6263
E-mail: fengcg@sioc.ac.cn
lingq@sioc.ac.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202660.

phine ligands, BINAP (**L1**), MeO-BIPHEP (**L2**), and SIPHOS-PE (**L3**), were examined, low yields (<15%) and low levels of enantioselectivity (23–61% *ee*) were observed (Table 1, entries 1, 3, and 5). When the reactions were carried out at 100°C, a common reaction temperature for reactions involving phosphine ligands, the results were worse (Table 1, entries 2, 4, and 6). Then we turned our attention to the chiral diene ligands. The use of chiral diene **L4** gave the product with a very high *ee* value (99%), albeit in moderate yield (50%; Table 1, entry 7). High yields could be obtained by using chiral ligands **L5** and **L6**, however, low levels of enantioselectivity were obtained (<65% *ee*; Table 1, entries 8 and 9). Using diene **L4**, attempts to further improve the yield by varying solvent, base, and temperature proved unsuccessful (Table 1, entries 10–15). We reasoned that the low yield probably originates from the deactivation of the rhodium catalyst, through its binding to the alkene moiety of adduct **3aa**, and the side products generated through the hydrolysis of trifluoroborate **2a**. To our delight, when freshly prepared [{Rh(OH)(**L4**)}$_2$] was used as a more active catalyst,[12] the yield significantly improved and reached 97% (Table 1, entry 16). Even with the use of a lower catalyst loading (1 mol% Rh), the product was still obtained in 79% yield with 99% *ee* (Table 1, entry 18).

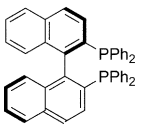
Table 1. Optimization of reaction conditions.[a]



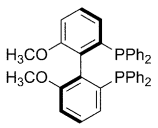
1a **2a** **3aa**

Entry	Catalyst	*T* [°C]	Base	Yield [%][e]	*ee* [%][f]
1	**L1**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	Et_3N	8	23
2	**L1**/[{RhCl(C_2H_4)$_2$}$_2$]	100	Et_3N	4	53
3	**L2**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	Et_3N	4	9
4	**L2**/[{RhCl(C_2H_4)$_2$}$_2$]	100	Et_3N	trace	–
5	**L3**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	Et_3N	13	61
6	**L3**/[{RhCl(C_2H_4)$_2$}$_2$]	100	Et_3N	trace	–
7	**L4**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	Et_3N	50	99
8	**L5**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	Et_3N	69	64
9	**L6**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	Et_3N	92	15[g]
10	**L4**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	DIEA	46	95
11	**L4**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	pyridine	8	95
12	**L4**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	KOH	43	96
13	**L4**/[{RhCl(C_2H_4)$_2$}$_2$]	45	Et_3N	38	95
14	**L4**/[{RhCl(C_2H_4)$_2$}$_2$]	60	Et_3N	37	96
15[b]	**L4**/[{RhCl(C_2H_4)$_2$}$_2$]	RT	Et_3N	58	71
16[c]	[{Rh(OH)(**L4**)}$_2$]	RT	Et_3N	97	99
17[c]	[{Rh(OH)(**L4**)}$_2$]	RT	–	42	99
18[d]	[{Rh(OH)(**L4**)}$_2$]	RT	Et_3N	79	99

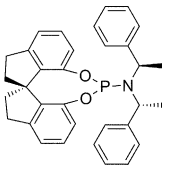
[a] Unless noted otherwise, reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), [{RhCl(C_2H_4)$_2$}$_2$] (0.005 mmol), ligand (0.011 mmol), catalytic amount of KOH (0.011 mmol) and 2 equiv of base in toluene/H_2O (10/1, 2.2 mL). [b] 1,4-Dioxane was used instead of toluene. [c] [{Rh(OH)(**L4**)}$_2$] (0.005 mmol) was used as rhodium catalyst and without adding KOH. [d] [{Rh(OH)(**L4**)}$_2$] (0.001 mmol) was used as rhodium catalyst and without adding KOH. [e] Yield of isolated product. [f] Determined by HPLC analysis, using a chiral stationary phase. [g] The sense of asymmetric induction was opposite that observed in reactions associated with other entries in this table. DIEA = *N*,*N*-diisopropylethylamine.



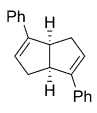
L1 (*R*)-BINAP



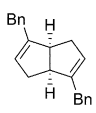
L2 (*R*)-MeO-BIPHEP



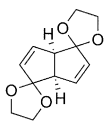
L3 (*R*)-SIPHOS-PE



(*S*,*S*)-**L4**



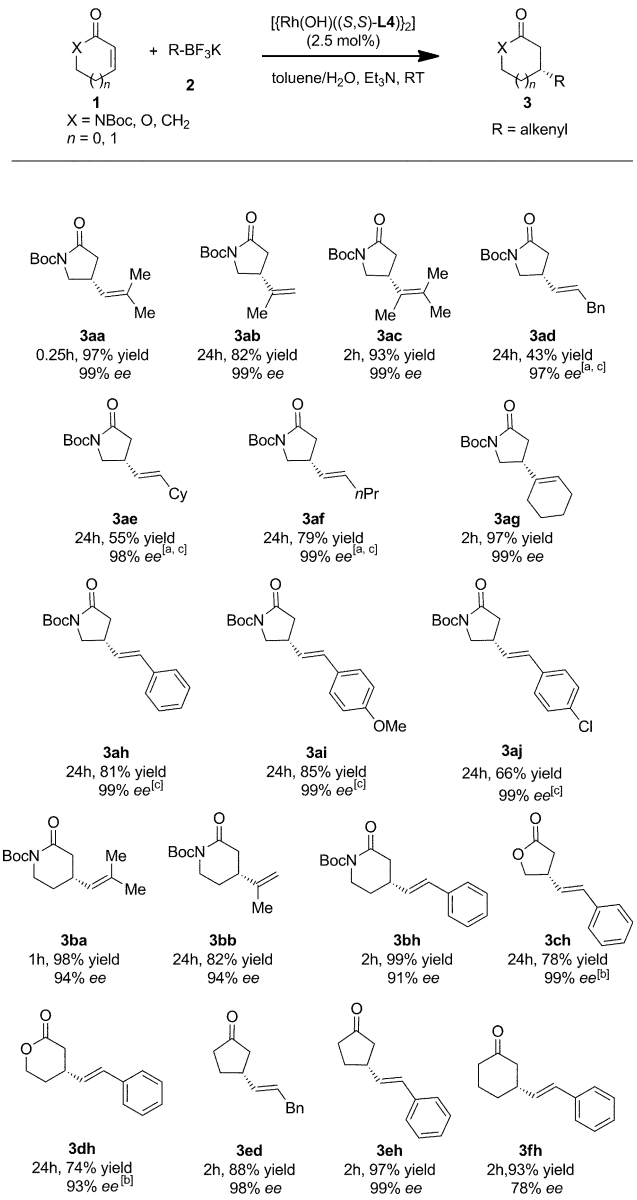
(*S*,*S*)-**L5**



(*R*,*R*)-**L6**

With optimized reaction conditions established (Table 1, entry 17), the reaction scope was examined (Scheme 2). The reactions of a variety of alkenyltrifluoroborates with lactam **1a** were successful and products were obtained in moderate to excellent yields (43–97%), with excellent levels of enantioselectivity (97–99% *ee*). Both steric and electronic properties of alkenyltrifluoroborates affected the yield and the enantioselectivity. The use of substituted alkenyltrifluoroborates gave products that were generally obtained in higher yield, therefore showing that increased steric hindrance is beneficial to the reaction. For example, very high yields were observed in the conjugate addition reaction of 2,2-dimethyl-substituted and 1,2,2-trimethyl-substituted alkenyltrifluoroborates (**3aa** and **3ac**). Alkenyltrifluoroborates that were relatively electron rich gave higher yields. In comparison with the conjugate addition reaction of 2-phenyl-alkenyltrifluoroborate, the reaction of a substrate containing an electron-donating methoxy group on the phenyl ring gave a slightly higher yield (85%; compare **3ah** with **3ai**); however, reaction of a substrate containing an electron-withdrawing chloride group on the phenyl ring gave a lower yield (66%; compare **3ah** with **3aj**). When a six-membered lactam was used, the levels of enantioselectivity were slightly lower although the yields remained high (**3ba**, **3bb**, and **3bh**). When the reaction of α,β-unsaturated lactones was investigated, a different combination of solvent and base was found to be optimal. The combination of toluene and Et_3N was replaced by the combination of dioxane and KF and in doing so, the yields were satisfactory, and again the levels of enantioselectivity observed for 5-membered lactones were higher than those observed for 6-membered lactones (compare **3ch** with **3dh**). As expected, the use of the more reactive α,β-unsaturated ketones led to high yields, although only the 5-membered 2-cyclopentenone gave excellent levels of enantioselectivity (98–99%; compare **3ed**, **3eh**, and **3fh**).

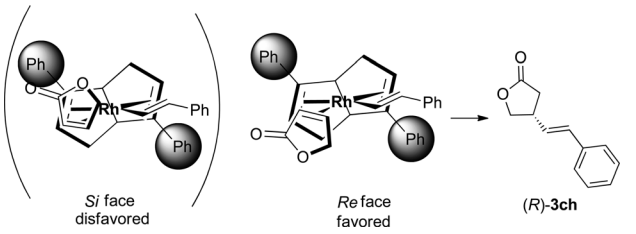
The absolute configurations of **3ch**, **3eh**, and **3fh** were assigned as *R* by comparison of their optical rotation with those in the literature;[13] the configuration of the products is in agreement with the stereochemistry-defining model for the arylation of enones that was described by Hayashi et al.[14] Using the conjugate addition reaction of potassium 2-(*E*)-phenylethenyltrifluoroborate and [5*H*]-furan-2-one in the presence of the rhodium catalyst bearing the ligand (*S*,*S*)-**L4** as an example, the alkenylrhodium intermediate prefers to coordinate to the *Re* face of the lactone to minimize steric repulsions between the phenyl groups on the



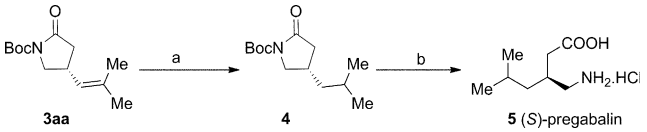
Scheme 2. Substrate scope of the rhodium-catalyzed asymmetric alkenylation reaction. Unless noted otherwise, reactions were carried out with **1** (0.2 mmol), **2** (0.4 mmol), [{Rh(OH)((*S*,*S*)-**L4**)}$_2$] (0.005 mmol), and Et_3N (56 μL) in toluene/H_2O (10:1, 2.2 mL). Yields are given for isolated products after column chromatography. The *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] Toluene/H_2O (50:1) was used. [b] Toluene and Et_3N were replaced by 1,4-dioxane and KF. [c] **2** (0.8 mmol) was used. Bn = benzyl, Cy = cyclohexyl.

diene and the lactone, thus leading to the desired product **3ch** with *R* configuration (Scheme 3). The configuration of other adducts were assigned as *R* by assuming a similar pathway.

The application of this method was demonstrated by a concise synthesis of (*S*)-pregabalin. As a 3-substituted analogue of γ-aminobutyric acid (GABA), which is a neurotransmitter, (*S*)-pregabalin, with the brand name Lyrica, is an anticonvulsant drug used to treat epilepsy and neuropathic pain.[15] Starting from conjugate-addition product **3aa**, a hydrogenation reaction followed by hydrolysis using 6M HCl afforded the desired (*S*)-pregabalin hydrochloride (**5**) in 96% yield over two steps (Scheme 4).

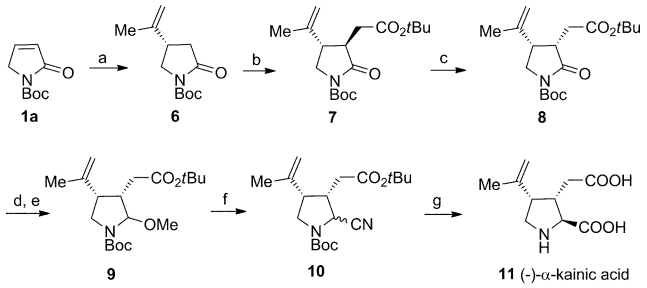


Scheme 3. Possible stereochemistry-defining pathway.



Scheme 4. Synthesis of (*S*)-pregabalin. Reaction conditions: a) 15 atm H_2, Pd/C, MeOH, RT (100%); b) 6M HCl, reflux (96%).

In a further application of our method, we decided to apply it in the synthesis (−)-α-kainic acid, a natural product first isolated in 1953 from the Japanese marine algae *digenea simplex*.[16] (−)-α-Kainic acid exhibits potent anthelmintic and neuroexcitatory activity, and currently has been widely used as a tool in neuropharmacology.[17] Because its limited availability has severely hampered research using this compound,[18] great efforts have been devoted to the total synthesis of (−)-α-kainic acid.[19] Our synthesis commenced with asymmetric alkenylation of lactam **1a**, as catalyzed by [{Rh(OH)((*R*,*R*)-**L4**)}$_2$], to furnish lactam **6** in 82% yield with 99% *ee* (Scheme 5). Next, alkylation of **6** gave *trans*-3,4-substituted ester **7**. The key *syn* relationship at C3/C4 in (−)-α-kainic acid was then easily established by inverting configuration at C3 through a dynamic protonation process. Treatment of **7** with LiHMDS followed by protonation with (−)-CSA at −78°C afforded the desired *cis*-ester **8** in 84% yield. Reduction of **8** by DIBAL-H followed by treatment with MeOH generated **9**, which when reacted with TMSCN in the presence of $BF_3{\cdot}OEt_2$ gave nitrile **10** as a 5:1 mixture of diastereomers.[19g] While benefitting from the epimerization of the undesired isomer during the basic hydrolysis process,[19g] the crude diastereomeric mixture of nitrile **10** was refluxed in 2M NaOH solution to afford the natural product (−)-α-kainic acid **11** in 82% yield. The total synthesis of (−)-α-kainic acid was therefore accomplished in seven steps from commercially available lactam **1a** in 40% yield, thus representing one of the most concise and efficient synthetic routes reported to date. Notably, the versatility of this synthetic strategy provides a convenient and easy access to a variety of kainic acid derivatives bearing different substitutions at the core pyrrolidine ring.



Scheme 5. Synthesis of (−)-α-kainic acid. Reaction conditions: a) potassium 2-propenyltrifluoroborate, [{Rh(OH)((*R*,*R*)-**L4**)}$_2$] (2.5 mol%), Et_3N, toluene/H_2O, RT (82%); b) LiHMDS, THF, −78°C; *tert*-butyl 2-bromoacetate, THF, −78°C (91%); c) LiHMDS, THF, −78°C; (−)-CSA, THF, −78°C (84%; with recovery of **7** 15%); d) DIBAL-H,THF, −78°C; e) PPTS, MeOH, 0°C (78%, two steps); f) TMSCN, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C (99%); g) NaOH, H_2O, reflux (82%). CSA = camphorsulfonic acid, DIBAL-H = diisobutylaluminum hydride, TMS = trimethylsilyl, LiHMDS = lithium hexamethyldisilazide, PPTS = pyridinium *p*-toluenesulfonate.

In summary, we have developed a rhodium-catalyzed asymmetric conjugate-addition reaction of potassium alkenyltrifluoroborates and α,β-unsaturated carbonyl compounds by using a rhodium–diene complex as a catalyst. Under optimized reaction conditions, the reactions gave products with moderate to excellent yields with high levels of enantioselectivity. The utility of this methodology was demonstrated by a concise synthesis of (*S*)-pregabalin and (−)-*α*-kainic acid. Further synthetic applications to the synthesis of natural products and pharmaceutical agents are currently in progress.[20]

Experimental Section

Typical procedure for the conjugate addition of potassium trifluoroborates: Under argon atmosphere, a mixture of **1** (0.2 mmol), potassium alkenyltrifluoroborate **2** (0.4 or 0.8 mmol), [{Rh(OH)((*S*,*S*)-**L4**)}$_2$] (1.9 mg, 0.005 mmol, 5 mol% Rh), H_2O (0.2 mL) and Et_3N (56 μL) in toluene (2 mL) was stirred at room temperature for 2—24 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford the desired product **3**. The *ee* value was determined by HPLC analysis using a chiral stationary phase.

Acknowledgements

We thank Dr. Han-Qing Dong for his help in the preparation of this manuscript. This work was supported by National Natural Science Foundation of China (21002112), the Major State Basic Research Development Program (2010CB833302), and the Shanghai Municipal Committee of Science and Technology (11431920300).

Keywords: alkenylation · asymmetric catalysis · conjugate addition · diene ligands · rhodium

[1] For reviews, see: a) T. Hayashi, *Synlett* **2001**, 879; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; c) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169; d) C. Gennari, C. Monti, U. Piarulli, *Pure Appl. Chem.* **2006**, *78*, 303; e) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279; f) H. J. Edwards, J. D. Hargrave, S. D. Penrose, C. G. Frost, *Chem. Soc. Rev.* **2010**, *39*, 2093.

[2] *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine, and Materials*, 2nd ed. (Ed: D. G. Hall), Wiley-VCH, Weinheim, **2011**.

[3] Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.

[4] a) Y. Takaya, M. Ogasawara, T. Hayashi, *Tetrahedron Lett.* **1998**, *39*, 8479; b) A. Duursma, J. G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045; c) R. T. Stemmler, C. Bolm, *J. Org. Chem.* **2005**, *70*, 9925; d) G. Lalic, E. J. Corey, *Tetrahedron Lett.* **2008**, *49*, 4894; e) K. Okamoto, T. Hayashi, V. H. Rawal, *Org. Lett.* **2008**, *10*, 4387; f) R. Shintani, Y. Ichikawa, K. Takatsu, F.-X. Chen, T. Hayashi, *J. Org. Chem.* **2009**, *74*, 869; g) C. M. König, B. Gebhardt, C. Schleth, M. Dauber, U. Koert, *Org. Lett.* **2009**, *11*, 2728; h) T. Gendrineau, J.-P. Genet, S. Darses, *Org. Lett.* **2009**, *11*, 3486; i) B. Gebhardt, C. M. Koenig, C. Schleth, M. Dauber, U. Koert, *Chem. Eur. J.* **2010**, *16*, 5934; j) Y. Wang, X. Hu, H. Du, *Org. Lett.* **2010**, *12*, 5482; k) G. Pattison, G. Piraux, H. W. Lam, *J. Am. Chem. Soc.* **2010**, *132*, 14373; l) G. Chen, J. Gui, L. Li, J. Liao, *Angew. Chem.* **2011**, *123*, 7823; *Angew. Chem. Int. Ed.* **2011**, *50*, 7681; m) T. Thaler, L.-N. Guo, A. K. Steib, M. Raducan, K. Karaghiosoff, P. Mayer, P. Knochel, *Org. Lett.* **2011**, *13*, 3182; n) B. M. Trost, A. C. Burns, T. Tautz, *Org. Lett.* **2011**, *13*, 4566.

[5] a) V. Hickmann, M. Alcarazo, A. Fürster, *J. Am. Chem. Soc.* **2010**, *132*, 11042; b) V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2011**, *133*, 13471.

[6] For rhodium-catalyzed asymmetric conjugate addition of alkenyl silicon and zirconium reagents, see: a) S. Oi, Y. Honma, Y. Inoue, *Org. Lett.* **2002**, *4*, 667; b) S. Oi, A. Taira, Y. Honma, Y. Inoue, *Org. Lett.* **2003**, *5*, 97; c) Y. Otomaru, T. Hayashi, *Tetrahedron: Asymmetry* **2004**, *15*, 2647; d) Y. Nakao, J. Chen, H. Imanaka, T. Hiyama, Y. Ichikawa, W.-L. Duan, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 9137; e) S. Oi, T. Sato, Y. Inoue, *Tetrahedron Lett.* **2004**, *45*, 5051.

[7] For copper-catalyzed asymmetric conjugate addition of alkenylmetallic reagents, see: a) A. El-Batta, T. R. Hage, S. Plotkin, M. Bergdahl, *Org. Lett.* **2004**, *6*, 107; b) A. Alexakis, V. Albrow, K. Biswas, M. d'Augustin, O. Prieto, S. Woodward, *Chem. Commun.* **2005**, 2843; c) K.-S. Lee, A. H. Hoveyda, *J. Org. Chem.* **2009**, *74*, 4455; d) D. Müller, C. Hawner, M. Tissot, L. Palais, A. Alexakis, *Synlett* **2010**, 1694; e) D. Müller, M. Tissot, A. Alexakis, *Org. Lett.* **2011**, *13*, 3040; f) D. Müller, A. Alexakis, *Org. Lett.* **2012**, *14*, 1842.

[8] For reviews on organotrifluoroborates, see: a) G. A. Molander, R. Figueroa, *Aldrichimica Acta* **2005**, *38*, 49; b) H. A. Stefani, R. Cella, A. S. Vieira, *Tetrahedron* **2007**, *63*, 3623; c) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275; d) S. Darses, J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288.

[9] a) M. Pucheault, S. Darses, J. P. Genet, *Tetrahedron Lett.* **2002**, *43*, 6155; b) M. Pucheault, S. Darses, J. P. Genet, *Eur. J. Org. Chem.* **2002**, 3552.

[10] For reviews of chiral diene ligands, see: a) J. B. Johnson, T. Rovis, *Angew. Chem.* **2008**, *120*, 852; *Angew. Chem. Int. Ed.* **2008**, *47*, 840; b) C. Defieber, H. Grutzmacher, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4558; *Angew. Chem. Int. Ed.* **2008**, *47*, 4482; c) R. Shintani, T. Hayashi, *Aldrichimica Acta* **2009**, *42*, 31; d) C.-G. Feng, M.-H. Xu, G.-Q. Lin, *Synlett* **2011**, 1345.

[11] C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C.-G. Feng, G.-Q. Lin, *Org. Lett.* **2011**, *13*, 788.

[12] Z. Cui, H.-J. Yu, R.-F. Yang, W.-Y. Gao, C.-G. Feng, G.-Q. Lin, *J. Am. Chem. Soc.* **2011**, *133*, 12394.

[13] See the Support Information for details.

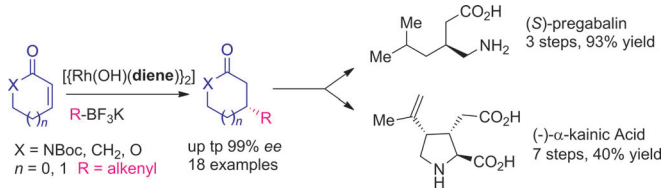
[14] T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508.
[15] For selected recent syntheses of pregabalin, see: a) T. Mita, K. Sasaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 514; b) A. Armstrong, N. J. Convine, M. E. Popkin, *Synlett* **2006**, 1589; c) V. Rodríguez, L. Quintero, F. Sartillo-Piscil, *Tetrahedron Lett.* **2007**, *48*, 4305; d) S. Poe, M. Kobaslija, T. McQuade, *J. Am. Chem. Soc.* **2007**, *129*, 9216; e) T. Ok, A. Jeon, J. Lee, J. H. Lim, C. S. Hong, H.-S. Lee, *J. Org. Chem.* **2007**, *72*, 7390; f) Z. Hamerŝak, I. Stipetić, A. Avdagić, *Tetrahedron: Asymmetry* **2007**, *18*, 1481; g) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307; h) M. Ordóñez, C. Cativiela, *Tetrahedron: Asymmetry* **2007**, *18*, 3; i) C. A. Martinez, S. Hu, Y. Dumond, J. Tao, P. Kelleher, L. Tully, *Org. Process Res. Dev.* **2008**, *12*, 392; j) O. Bassas, J. Huuskonen, K. Rissanen, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2009**, 1340; k) J.-M. Liu, X. Wang, Z.-M. Ge, Q. Sun, T.-M. Cheng, R.-T. Li, *Tetrahedron* **2011**, *67*, 636.
[16] S. Murakami, T. Takemoto, Z. Shimizu, *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.
[17] E. G. MacGeer, J. W. Olney, P. L. MacGeer, *Kainic Acid as a Tool in Neurobiology*, Raven, New York, **1978**.
[18] a) J.-F. Tremblay, *Chem. Eng. News* **2000**, *78*, 14; b) J.-F. Tremblay, *Chem. Eng. News* **2001**, *79*, 19.
[19] Selected recent syntheses of (+)- and (−)-α-kainic acid, see: a) Y. C. Jung, C. H. Yoon, E. Turos, K. S. Yoo, K. W. Jung, *J. Org. Chem.* **2007**, *72*, 10114; b) K. Tomooka, T. Akiyama, P. Man, M. Suzuki, *Tetrahedron Lett.* **2008**, *49*, 6327; c) M. S. Majik, P. S. Parameswaran, S. G. Tilve, *J. Org. Chem.* **2009**, *74*, 3591; d) A. Farwick, G. Helmchen, *Org. Lett.* **2010**, *12*, 1108; e) K. Kitamoto, M. Sampei, Y. Nakayama, T. Sato, N. Chida, *Org. Lett.* **2010**, *12*, 5756; f) G. Lemie're, S. Sedehizadeh, J. Toueg, N. Fleary-Roberts, J. Clayden, *Chem. Commun.* **2011**, *47*, 3745; g) S. Takita, S. Yoloshima, T. Fukuyama, *Org. Lett.* **2011**, *13*, 2068; h) T. Kamon, Y. Irifune, T. Tanaka, T. Yoshimitsu, *Org. Lett.* **2011**, *13*, 2674; i) M. A. Lowe, M. Ostovar, S. Ferrini, C. C. Chen, P. G. Lawrence, F. Fontana, A. A. Calabrese, V. K. Aggarwal, *Angew. Chem.* **2011**, *123*, 6494; *Angew. Chem. Int. Ed.* **2011**, *50*, 6370; j) G. Wei, J. M. Chalker, T. Cohen, *J. Org. Chem.* **2011**, *76*, 7912; k) P. J. Parsons, S. P. G. Rushton, R. R. Panta, A. J. Murray, M. P. Coles, J. Lai, *Tetrahedron* **2011**, *67*, 10267.
[20] During the preparation of this manuscript, a rhodium-catalyzed conjugate-addition reaction of alkenylboronic acids to cyclic enones with similar bicyclo[3.3.0]octa-2,5-diene ligands was reported: S. Helbig, K. V. Axenov, S. Tussetschläger, W. Frey, S. Laschat, *Tetrahedron Lett.* **2012**, *53*, 3506.

Received: July 26, 2012
Published online: ■■ ▮▮, 0000

Asymmetric Alkenylation

H.-J. Yu, C. Shao, Z. Cui, C.-G. Feng, G.-Q. Lin** ..... ▮▮▮▮–▮▮▮▮

Highly Enantioselective Alkenylation of Cyclic α,β-Unsaturated Carbonyl Compounds as Catalyzed by a Rhodium–Diene Complex: Application to the Synthesis of (*S*)-Pregabalin and (−)-α-Kainic Acid



Rhod to addition: An efficient asymmetric conjugate-addition reaction of alkenyltrifluoroborates and α,β-unsaturated carbonyl compounds, as catalyzed by a rhodium–diene complex, was developed. The products were obtained in high yield and high levels of enantioselectivity. The methodology was applied to a concise synthesis of (*S*)-pregabalin and (−)-α-kainic acid (see scheme).

