

# Enantioselective synthesis of tricyclic amino acid derivatives based on a rigid 4-azatricyclo[5.2.1.0<sup>2,6</sup>]decane skeleton

Matthias Breuning<sup>\*1</sup>, Tobias Häuser<sup>1</sup>, Christian Mehler<sup>1</sup>,  
Christian Däschlein<sup>2</sup>, Carsten Strohmann<sup>2</sup>, Andreas Oechsner<sup>3</sup>  
and Holger Braunschweig<sup>3</sup>

## Full Research Paper

Open Access

### Address:

<sup>1</sup>Institut für Organische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany, <sup>2</sup>Anorganische Chemie, Universität Dortmund, Otto-Hahn-Str. 6, 44227 Dortmund, Germany and <sup>3</sup>Institut für Anorganische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany

### Email:

Matthias Breuning<sup>\*</sup> - breuning@chemie.uni-wuerzburg.de

\* Corresponding author

### Keywords:

amino acid; enantioselective synthesis; norbornane; polycyclic compounds; pyrrolidine

Beilstein Journal of Organic Chemistry 2009, 5, No. 81.

doi:10.3762/bjoc.5.81

Received: 20 August 2009

Accepted: 26 October 2009

Published: 21 December 2009

Associate Editor: N. Sewald

© 2009 Breuning et al; licensee Beilstein-Institut.

License and terms: see end of document.

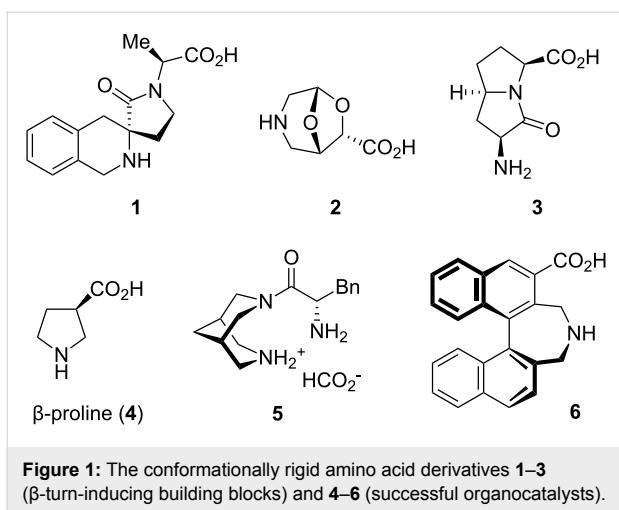
## Abstract

An enantioselective route to four tricyclic amino acids and *N*-tosylamides, composed of a central norbornane framework with a 2-*endo*,3-*endo*-annelated pyrrolidine ring and a 5-*endo*-C<sub>1</sub> or -C<sub>2</sub> side chain, has been developed. A key intermediate was the chiral, *N*-Boc-protected ketone (1*R*,2*S*,6*S*,7*R*)-4-azatricyclo[5.2.1.0<sup>2,6</sup>]decan-8-one, available from inexpensive *endo*-carbic anhydride in five steps and 47% yield. The rigid scaffold makes these amino acid derivatives promising candidates for  $\beta$ -turn-inducing building blocks in peptidomimetics and for chiral auxiliaries in asymmetric organocatalysis.

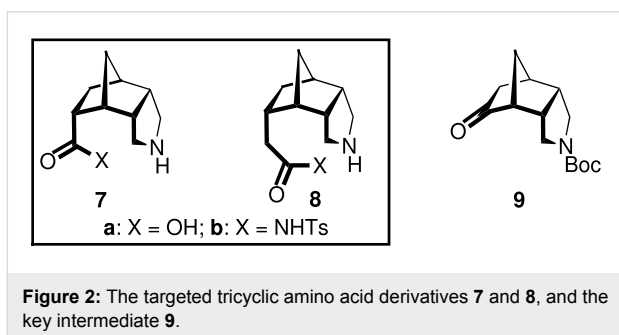
## Introduction

Unnatural amino acids with a rigid bowl-shaped backbone have received considerable interest in recent years. Incorporated in peptides or proteins, they may increase the metabolic stability and allow the introduction of novel structural motifs [1-4].  $\beta$ -Turns, for example, result if conformationally constrained spiro- or bicyclic amino acids such as **1** [5], **2** [6], and **3** [7,8] are embedded in peptidomimetics (Figure 1). Enantioselective organocatalysis [9-17] is another field of application for

conformationally rigid amino acid derivatives. In this context, focus was also put on derivatives in which the activating acidic group is anchored at a more remote position of the molecule, but still in close spatial proximity to the amino function. Examples are  $\beta$ -proline (**4**) [18,19], the bispidinium salt **5** [20], and the binaphthyl-derived amino acid **6** [21-23], which provided excellent enantioselectivities in several aldol and Mannich reactions.



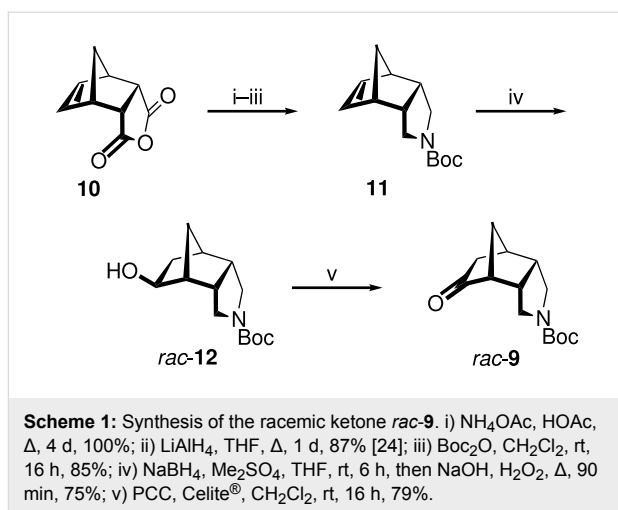
Our studies targeted the chiral, tricyclic amino acid derivatives **7** and **8** (Figure 2), which possess a central norbornane framework equipped with a 2-*endo*,3-*endo*-annelated pyrrolidine ring. Due to the constrained, bowl-shaped backbone, these compounds may possess high potential as  $\beta$ -turn-inducing peptide building blocks and as bifunctional organocatalysts. In this paper we report on the first enantioselective synthesis of **7** and **8**, which was achieved via the chiral ketone **9** as the key intermediate.



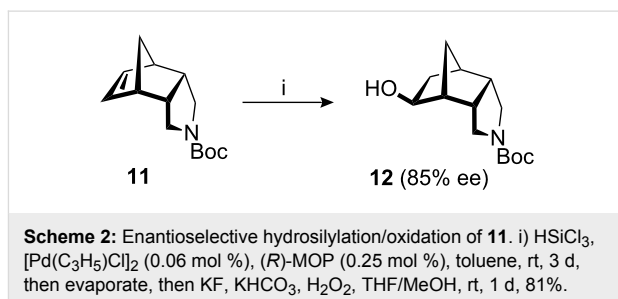
## Results and Discussion

The key intermediate, the tricyclic amino ketone **9**, was first prepared in racemic form starting from inexpensive *endo*-carbic anhydride (**10**, Scheme 1). Conversion of the succinyl anhydride moiety in **10** into the pyrrolidine ring in **11** was accomplished in three steps and 74% yield by imide formation, reduction [24], and N-protection. Hydroboration/oxidation of the alkene function of **11** delivered the *exo*-configured alcohol *rac*-**12**, which was oxidized with PCC furnishing *rac*-**9** in 79% yield.

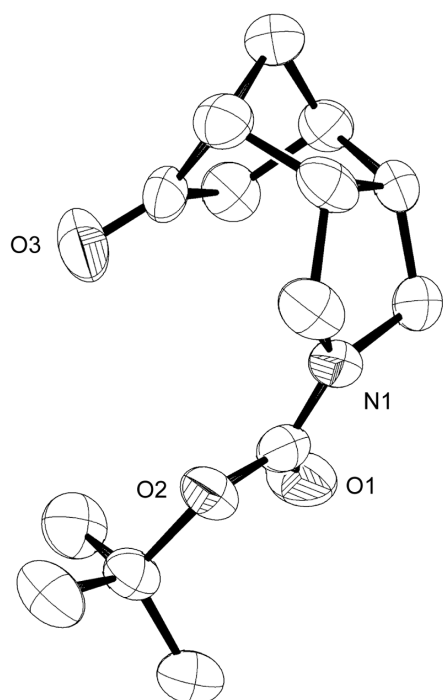
The asymmetric synthesis of the ketone **9** was realized by enantioselective hydration of the *meso*-alkene **11** using Hayashi's method (Scheme 2) [25–30]: Hydrosilylation with



trichlorosilane in the presence of a catalytic amount of  $[\text{Pd}(\text{C}_3\text{H}_5\text{Cl})_2]$  and (*R*)-MOP [(*R*)-2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl], followed by  $\text{SiCl}_3/\text{OH}$  exchange, delivered the *exo*-alcohol **12** in 81% yield and 85% ee, as determined from the (*S*)- and (*R*)-Mosher esters of **12**. After oxidation (see Scheme 1), the chiral ketone **9** was thus available in overall five steps and 47% yield from **10**. The X-ray crystal structure of **9** is shown in Figure 3.



Initial studies on the installation of the functionalized  $\text{C}_1$  side chain, as required for the amino acid derivatives **7**, were done on racemic material and aimed at an oxidation of the alkene *rac*-**13** (Scheme 3), which was available from the ketone *rac*-**9** either by Wittig reaction or by a Tebbe-type olefination [31] using  $\text{Mg}$ ,  $\text{TiCl}_4$ , and  $\text{CH}_2\text{Cl}_2$ . Hydroboration/oxidation of *rac*-**13** occurred highly diastereoselectively on the *exo*-side providing the desired *endo*-alcohol *rac*-**14**, as determined by NOE measurements. Further oxidation with PCC gave the aldehyde *rac*-**15**, albeit in low 13% overall yield from *rac*-**9**. As an alternative, the epoxidation of *rac*-**13** with MCPBA was investigated, which delivered the spirocyclic *exo*-configured epoxide *rac*-**16** in 46% overall yield from *rac*-**9** as the sole diastereomer. Lewis acid-catalyzed rearrangement of *rac*-**16** with  $\text{BF}_3$  etherate [32] furnished the desired aldehyde *rac*-**15** in 26% yield (12% overall yield from *rac*-**9**) and the tetracyclic

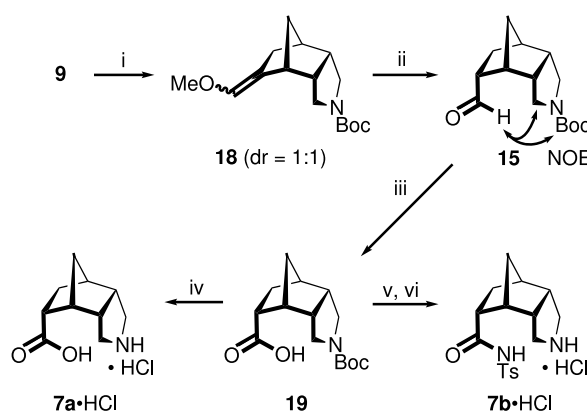


**Figure 3:** X-ray crystal structure of **9**. X-ray data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 743050).

*N,O*-acetal *rac*-**17** in 35% yield. The latter compound is presumably formed from *rac*-**15** by a Lewis acid-catalyzed, intramolecular, and thus proximity-facilitated tandem hydride transfer/cyclization sequence [33].

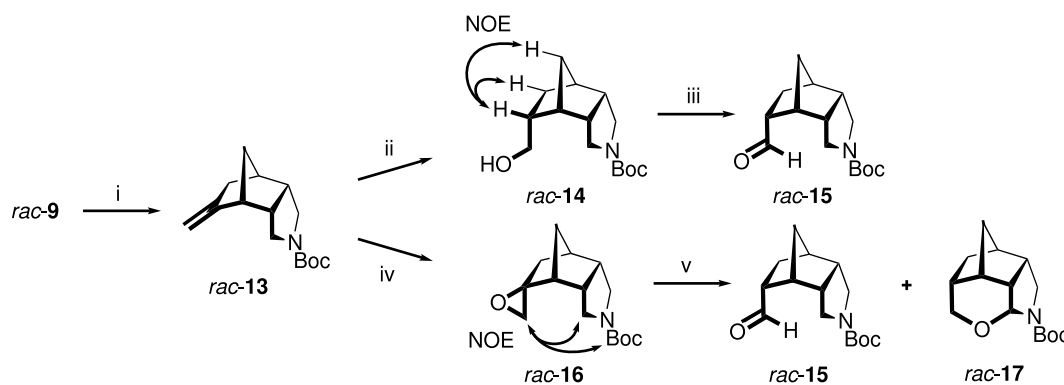
Since the yields of *rac*-**15** from the alkene *rac*-**13** were low, we turned our attention to an alternative approach via the enol ether **18**, which was available from **9** as a 1:1 mixture of *E/Z*-isomers by Wittig reaction with MeOCH=PPh<sub>3</sub> (Scheme 4). The

selective hydrolysis of the enol ether moiety in **18** in the presence of the *N*-Boc-protective group was achieved by using trichloroacetic acid. The desired *endo*-configured aldehyde **15** was thus available in only two steps in good 64% overall yield from **9**. After oxidation of **15** to the acid **19**, the target amino acid **7a**•HCl was obtained by *N*-deprotection with aqueous HCl in overall four steps and 38% yield from **9**. The *N*-tosylamide **7b**•HCl was accessed from **19** by condensation with TsNH<sub>2</sub> under Steglich conditions followed by *N*-deprotection with ethereal HCl (overall five steps and 12% yield from **9**).



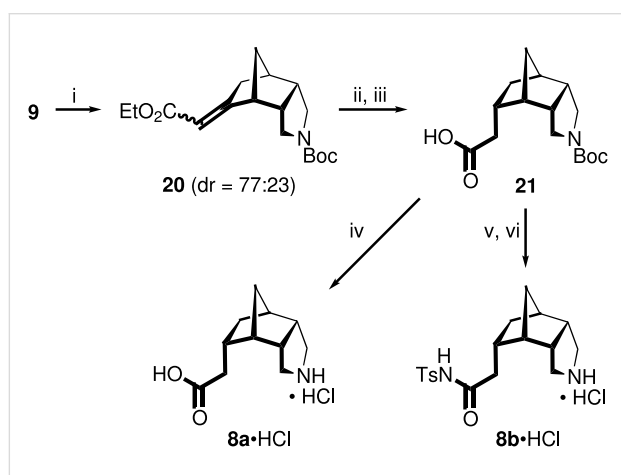
**Scheme 4:** Assembly of the amino acid **7a**•HCl and the *N*-tosylamide **7b**•HCl. i) MeOCH<sub>2</sub>PPh<sub>3</sub><sup>+</sup>Cl<sup>-</sup>, *t*-BuOK, toluene/THF, rt, 1 d, 84%; ii) Cl<sub>3</sub>CCO<sub>2</sub>H, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.5 h, 76%; iii) NaClO<sub>2</sub>, H<sub>2</sub>O<sub>2</sub>, KH<sub>2</sub>PO<sub>4</sub>, H<sub>2</sub>O/MeCN, rt, 6 h, 75%; iv) HCl, H<sub>2</sub>O, Δ, 1 d, 79%; v) TsNH<sub>2</sub>, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 d, 64%; vi) HCl, Et<sub>2</sub>O, MeOH, rt, 3 h, 38%.

The preparation of the amino acid **8a**•HCl and the *N*-tosylamide **8b**•HCl required the attachment of an *endo*-oriented acetic acid substituent at the position of the keto group in **9** (Scheme 5). Initial attempts to introduce such a side chain by Wittig or Horner-Wadsworth-Emmons reactions, for example

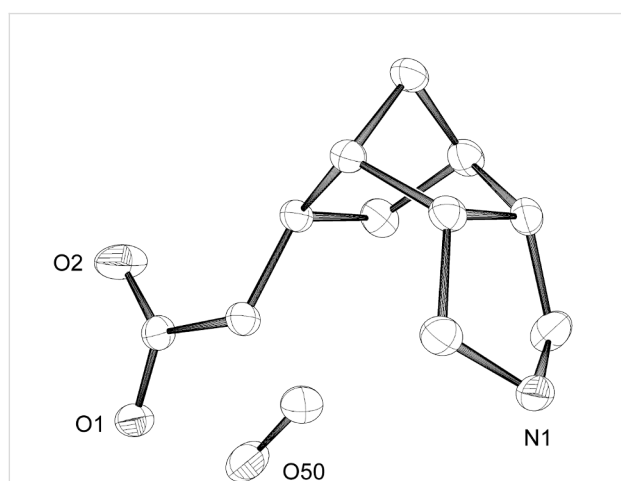


**Scheme 3:** Initial route to the aldehyde *rac*-**15**. i) MePPh<sub>3</sub><sup>+</sup>Br<sup>-</sup>, *t*-BuOK, toluene, Δ, 7 h, 77% or Mg, TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → rt, 2 h, 55%; ii) NaBH<sub>4</sub>, Me<sub>2</sub>SO<sub>4</sub>, THF, 0 °C → rt, 18 h, then NaOH, H<sub>2</sub>O<sub>2</sub>, rt, 3 h, 34%; iii) PCC, CH<sub>2</sub>Cl<sub>2</sub>, rt, 6 h, 51%; iv) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h, 60%; v) BF<sub>3</sub>•OEt<sub>2</sub>, toluene, 0 °C, 5 min, 35% (*rac*-**17**) and 26% (*rac*-**15**).

with  $\text{MeO}_2\text{CCH}=\text{PPh}_3$  or  $\text{MeO}_2\text{CCH}_2\text{P}(\text{O})(\text{OEt})_2/n\text{-BuLi}$ , failed. By contrast, Peterson-type olefination using  $\text{TMSCH}_2\text{CO}_2\text{Et/LDA}$  cleanly afforded the  $\alpha,\beta$ -unsaturated ester **20** as a 77:23 mixture of the *E/Z*-isomers in 50% yield. The reduction of the conjugated double bond with Mg in methanol furnished, after saponification, the *endo*-configured acid **21** as a single diastereomer. The further conversion of **21** into the target molecules was carried out in analogy to the preparation of **7a/b**·HCl from **19** (see Scheme 4), giving **8a**·HCl in overall 24% yield from **9** (four steps) and **8b**·HCl in overall 10% yield (five steps). The required *endo*-orientation of the acetic acid moiety in **8a**·HCl was confirmed by the X-ray structure of the corresponding free base **8a**·MeOH (Figure 4).



**Scheme 5:** Preparation of the amino acid **8a**·HCl and the *N*-tosylamide **8b**·HCl. i)  $\text{TMSCH}_2\text{CO}_2\text{Et}$ , LDA, THF,  $-78^\circ\text{C} \rightarrow \text{rt}$ , 19 h, 50%; ii) Mg, MeOH, rt, 16 h, 76%; iii) KOH, EtOH/ $\text{H}_2\text{O}$ ,  $\Delta$ , 1 d, 90%; iv) HCl,  $\text{H}_2\text{O}$ ,  $\Delta$ , 1 d, 71%; v)  $\text{TsNH}_2$ , DCC, DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 4 d, 72%; vi) HCl,  $\text{Et}_2\text{O}$ , rt, 20 h, 42%.



**Figure 4:** X-ray crystal structure of **8a**·MeOH. X-ray data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 742656).

A first evaluation of the bowl-shaped amino acid derivatives **7** and **8** in standard organocatalytic aldol and Mannich reactions showed that these compounds are capable of promoting these reactions, albeit with low yields and enantioselectivities. Further investigations on this issue and on the use of **7** and **8** as  $\beta$ -turns are in progress.

## Conclusion

The enantioselective syntheses of the bowl-shaped, tricyclic amino acids and *N*-tosylamides **7** and **8** were successfully accomplished in 9–10 steps starting with inexpensive *endo*-carbic anhydride (**10**). The key stereochemical step was the desymmetrization of the *meso*-alkene **11** using Hayashi's hydrosilylation/oxidation procedure, which provided the *endo*-alcohol **12** in 85% ee. The target molecules are promising candidates as  $\beta$ -turn-inducing building blocks in peptidomimetics and as chiral auxiliaries in organocatalysis.

## Supporting Information

### Supporting Information File 1

Full experimental details and characterization data for all new compounds.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-81-S1.pdf>]

### Supporting Information File 2

NMR spectra of all new compounds.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-81-S2.pdf>]

### Supporting Information File 3

Crystallographic data of the compounds **8a**·MeOH and **9**.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-81-S3.pdf>]

## References

- Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011. doi:10.1021/cr990120t
- Komarov, I. V.; Grigorenko, A. O.; Turov, A. V.; Khilya, V. P. *Russ. Chem. Rev.* **2004**, *73*, 785–810. doi:10.1070/RC2004v073n08ABEH000912
- Gardiner, J.; Abell, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2365–2370. doi:10.1039/b406450j
- Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732. doi:10.1016/S0957-4166(99)00565-0
- Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 8098–8105. doi:10.1021/jo901480d
- Danieli, E.; Trabocchi, A.; Menchi, G.; Guarna, A. *Eur. J. Org. Chem.* **2007**, 1659–1668. doi:10.1002/ejoc.200600650
- Dietrich, E.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6988–6996. doi:10.1021/jo034739d

8. Ramana Rao, M. H. V.; Pinyol, E.; Lubell, W. D. *J. Org. Chem.* **2007**, *72*, 736–743. doi:10.1021/jo0616761
9. Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem.* **2008**, *120*, 6232–6265. doi:10.1002/ange.200705523  
*Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171. doi:10.1002/anie.200705523
10. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. doi:10.1021/cr0684016
11. Tanaka, F.; Barbas, C. F., III. *Aldol and Mannich-Type Reactions. In Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007; pp 19–55.
12. Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011. doi:10.1039/b517090g
13. List, B. *Chem. Commun.* **2006**, 819–824. doi:10.1039/b514296m
14. Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591. doi:10.1021/ar0300468
15. List, B. *Tetrahedron* **2002**, *58*, 5573–5590. doi:10.1016/S0040-4020(02)00516-1
16. Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495. doi:10.1016/S0040-4020(02)00122-9
17. List, B. *Synlett* **2001**, 1675–1686. doi:10.1055/s-2001-18074
18. Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630–9631. doi:10.1021/ja062950b
19. Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2008**, *130*, 875–886. doi:10.1021/ja074907+
20. Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654–5655. doi:10.1021/ja800839w
21. Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem.* **2005**, *117*, 3115–3117. doi:10.1002/ange.200500408  
*Angew. Chem., Int. Ed.* **2005**, *44*, 3055–3057. doi:10.1002/anie.200500408
22. Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem.–Asian J.* **2006**, *1*, 210–215. doi:10.1002/asia.200600077
23. Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465–5473. doi:10.1039/b809301f
24. Michaelis, S.; Blechert, S. *Chem.–Eur. J.* **2007**, *13*, 2358–2368. doi:10.1002/chem.200601183
25. Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354–362. doi:10.1021/ar990080f
26. Hayashi, T. *Catal. Today* **2000**, *62*, 3–15. doi:10.1016/S0920-5861(00)00404-1
27. Hayashi, T. *Catal. Surv. Jpn.* **1999**, *3*, 127–135. doi:10.1023/A:1019075719151
28. Hayashi, T. *Acta Chem. Scand.* **1996**, *50*, 259–266. doi:10.3891/acta.chem.scand.50-0259
29. Hayashi, T.; Uozumi, Y. *Pure Appl. Chem.* **1992**, *64*, 1911–1916. doi:10.1351/pac199264121911
30. Uozumi, Y.; Lee, S.-Y.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 7185–7188. doi:10.1016/S0040-4039(00)60868-7
31. Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* **2004**, *6*, 4961–4963. doi:10.1021/ol0478887
32. Basabe, P.; Delgado, S.; Marcos, I. S.; Diez, D.; Diego, A.; De Román, M.; Urones, J. G. *J. Org. Chem.* **2005**, *70*, 9480–9485. doi:10.1021/jo0515529
33. Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429–5431. doi:10.1021/ol0522283

## License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (<http://www.beilstein-journals.org/bjoc>)

The definitive version of this article is the electronic one which can be found at:  
[doi:10.3762/bjoc.5.81](https://doi.org/10.3762/bjoc.5.81)