Asymmetric Catalysis

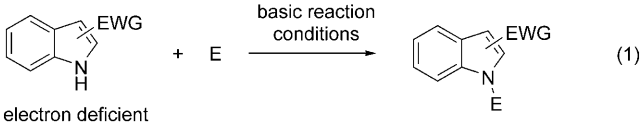
DOI: 10.1002/anie.201003919

Enantioselective Intramolecular Aza-Michael Additions of Indoles Catalyzed by Chiral Phosphoric Acids**

*Quan Cai, Chao Zheng, and Shu-Li You**

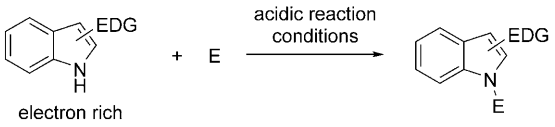
Chiral indole frameworks are widely distributed throughout natural products and pharmaceuticals.[1] In this scenario, enormous efforts have been devoted to the development of efficient syntheses of enantioenriched indole derivatives.[2] It has been well documented that the C3-position of an indole is the most reactive of the three reactive positions (N1, C2, C3). Therefore, considerable attention has been paid to the asymmetric C3 alkylation of indole.[3] Recently, the enantioselective C2 alkylation of indole was realized through an asymmetric Pictet–Spengler reaction,[4] alkylation of 2-indolyl trifluoroborate salts,[5] and Friedel–Crafts alkylation of 4,7-dihydroindoles.[6] However, the enantioselective N alkylation of an indole has rarely been explored,[7] despite the fact that the products are privileged structural motifs in natural alkaloids and biologically active compounds.[8]

Upon introduction of an electron-withdrawing group (EWG) on the indole core, the proton on the nitrogen atom becomes more acidic, therefore making the N position prone to alkylation under basic reaction conditions [Eq. (1), E = electrophile]. In taking advantage of this strategy, several groups have successfully realized the enantioselective N alkylation of indoles.[7] However, in most of the reported catalytic systems, indoles without electron-withdrawing groups were not tolerated, the only exception being in the work by Chen et al.[7c]

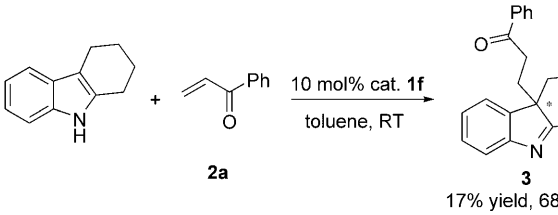


(1)

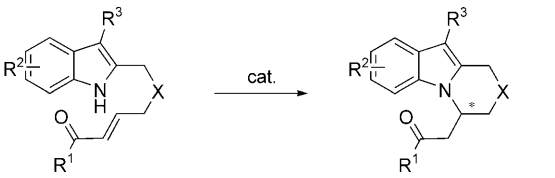
As part of our ongoing program on the asymmetric Friedel–Crafts alkylation of indoles,[2e] we recently explored the N alkylation of indoles by using chiral phosphoric acid catalysts [Eq. (2)]. We envisaged that installation of an electron-donating group (EDG) at the C3-position of the indole could increase the nucleophilicity of the indolyl nitrogen atom. However, this approach would have to avoid the C3 alkylation of the 3-substituted indoles to produce the indolenines, a strategy that has been demonstrated by several groups that employed transition-metal catalysis or organocatalysis.[9] For the initial investigation, the indolenine product was obtained from the tetrahydrocarbazole and enone in the presence of chiral phosphoric acid; the N-alkylation product was not observed [Eq. (3)]. Interestingly, when the intramolecular reaction was tested, the N-alkylation product was obtained chemoselectively [Eq. (4)], providing facile access to enantioenriched polycyclic indoles.[10] Herein we communicate our study on the chiral phosphoric acid catalyzed asymmetric, intramolecular Friedel–Crafts-type aza-Michael reaction of indoles and the preliminary mechanistic investigation.



(2)



(3)



(4)

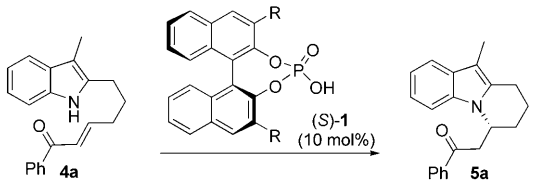
We first studied the cyclization of α,β-unsaturated ketone **4a** with various chiral phosphoric acids (entries 1–7, Table 1). To our delight, the aza-Michael addition product was obtained with promising chemoselectivity and enantioselectivity. Chiral phosphoric acid **1g** bearing triphenylsilyl groups proved to be the optimal catalyst, affording product **5a** in 96% yield and 89% *ee* (entry 7, Table 1). Additional screening of solvents (entries 7–9, Table 1) revealed that toluene was the best. When 4 Å molecular sieves (M.S.) were used as

[*] Q. Cai, C. Zheng, Prof. Dr. S.-L. You
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
Fax: (+86) 21-5492-5087
E-mail: slyou@mail.sioc.ac.cn
Homepage: http://shuliyou.sioc.ac.cn/

[**] We thank the National Natural Science Foundation of China (20732006, 20821002), the National Basic Research Program of China (973 Program 2010CB833300), and the Chinese Academy of Sciences for generous financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201003919.

Table 1: Optimization of the reaction conditions for the enantioselective aza-Michael reaction.[a]



Entry	R	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	4-$NO_2C_6H_4$ (**1a**)	toluene	RT	0.3	81	43
2	9-anthryl (**1b**)	toluene	RT	2	84	46
3	1-naphthyl (**1c**)	toluene	RT	12	72	22
4	1-pyrenyl (**1d**)	toluene	RT	2	83	16
5	4-biphenyl (**1e**)	toluene	RT	12	84	13
6	9-phenanthryl (**1f**)	toluene	RT	12	76	24
7	$SiPh_3$ (**1g**)	toluene	RT	2	96	89
8	$SiPh_3$ (**1g**)	CH_2Cl_2	RT	2	99	84
9	$SiPh_3$ (**1g**)	CCl_4	RT	1	73	85
10[d]	$SiPh_3$ (**1g**)	toluene	RT	1	98	91
11[d]	$SiPh_3$ (**1g**)	toluene	0	2	95	92
12[d]	$SiPh_3$ (**1g**)	toluene	−20	17	94	93

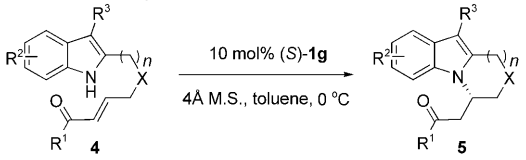
[a] Reaction conditions: 10 mol% (*S*)-**1**, 0.05 mol L^{-1} of **4a**. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Used 50 mg activated 4 Å M.S. (0.1 mmol **4a**).

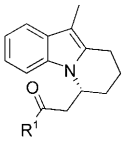
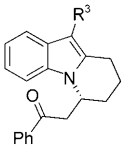
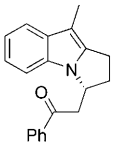
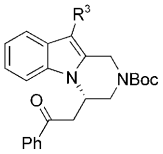
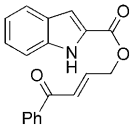
an additive, the reaction proceeded faster and with higher enantioselectivity (entry 10, Table 1). In general, lowering the temperature resulted in an increased *ee* value but a prolonged reaction time (entries 10–12, Table 1). Reactions at 0 °C led to optimal results in terms of both enantioselectivity and reaction time (entry 11, Table 1).

Under the optimized reaction conditions the substrate scope of this methodology was examined. In general, several kinds of polycyclic indoles could be synthesized in good yields and with good *ee* values (Table 2). Substituted phenyl enones bearing electron-donating or electron-withdrawing groups, as well as 2-naphthyl enone were suitable substrates for the aza-Michael reaction to afford 6,7,8,9-tetrahydropyrido[1,2-a]-indoles in 91–96% yields and 87–92% *ee* (entries 1–6, Table 2). Remarkably, various functionalities such as carbonyl and hydroxy groups, as well as aromatic rings could be tolerated in the C3 side chain (entries 7–12, Table 2) without affecting the yields and *ee* values. This methodology could also be used to construct the 2,3-dihydro-1*H*-pyrrolo[1,2-a]-indole ring system, the core structure of yurenamine,[10a] with a slightly decreased *ee* value (entry 13, Table 2). When the nitrogen-linked substrates **5n–o** were used, 1,2,3,4-tetrahydropyrazino[1,2-a]indole derivatives were obtained with excellent *ee* values after a longer reaction time (entries 14 and 15, Table 2). Furthermore, the reaction was completely inhibited by the introduction of an electron-withdrawing group, such as an ester, at C2-position of indole (entry 16, Table 2).

The combination of mechanistically distinct organocatalysis and transition-metal catalysis has enabled novel transformations and often reduces labor and waste.[11] Recently, we developed an efficient olefin cross-metathesis/intramolecular Friedel–Crafts alkylation sequence by using a ruthenium catalyst and a chiral phosphoric acid to construct polycyclic

Table 2: Substrate scope for the intramolecular aza-Michael reaction.[a]

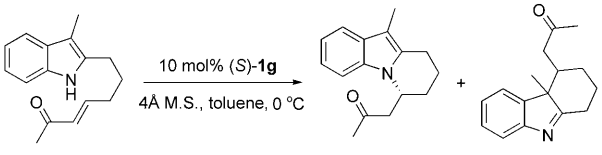


Entry	Product		*t* [h]	Yield [%][b]	*ee* [%][c]
1		**5a**: $R^1 = C_6H_5$	2	95	92
2		**5b**: $R^1 = 4\text{-}BrC_6H_4$	2	96	91
3		**5c**: $R^1 = 4\text{-}ClC_6H_4$	1.5	95	92
4		**5d**: $R^1 = 4\text{-}MeC_6H_4$	3	94	90
5		**5e**: $R^1 = 4\text{-}MeOC_6H_4$	4	93	91
6		**5f**: R^1 = 2-naphthyl	1.5	91	87
7		**5g**: R^3 = ethyl	2	91	91
8		**5h**: R^3 = propyl	3	94	89
9		**5i**: $R^3 = CH_2CH_2COCH_3$	3	96	93
10		**5j**: $R^3 = CH_2CH_2COPh$	4	83	93
11		**5k**: $R^3 = CH_2CH_2OH$	3	85	88
12		**5l**: R^3 = Bn	3	82	88
13[d]		**5m**	48	98	69
14[d]		**5n**: R^3 = Me	48	72	91
15[d]		**5o**: R^3 = Ph	384	76	93
16[d]		**4q**	no reaction		

[a] Reaction conditions: 10 mol% (*S*)-**1g**, 0 °C, 0.05 mol L^{-1} of **4** and activated 4 Å M.S. in toluene. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was carried out at room temperature. Boc = *tert*-butoxycarbonyl.

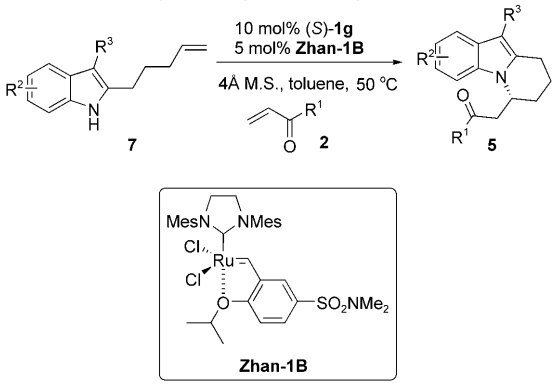
indoles.[12a] This combination of catalysts was also examined in this intramolecular aza-Michael addition. To our delight, when indolyl olefin **7** and the enone **2** (1.5 equiv) were heated in toluene at 50 °C with (*S*)-**1g** (10 mol%) and the ruthenium catalyst **Zhan-1B** (5 mol%), the desired products **5** were obtained in excellent yields and *ee* values (entries 1–8, Table 3).[13]

Interestingly, when **4p** was used as the substrate, both the N1-alkylation product **5p** and the C3-alkylation product **6** were obtained [Eq. (5)]. When heated in refluxing toluene with 10 mol% (*S*)-**1g**, compound **6** was converted into the aza-Michael addition product **5p** in 95% yield and 35% *ee*



(5)

Table 3: Substrate scope for sequential catalysis.[a]



Entry	R^2,R^3	R^1	Yield [%][b]	*ee* [%][c]
1	H, Me (**7a**)	Ph (**2a**)	89 (**5a**)	90
2	H, Me (**7a**)	4-BrC_6H_4 (**2b**)	80 (**5b**)	88
3	H, $CH_2CH_2COCH_3$ (**7d**)	Ph (**2a**)	92 (**5i**)	90
4	H, CH_2CH_2COPh (**7e**)	Ph (**2a**)	94 (**5j**)	90
5	H, CH_2CH_2OH (**7f**)	Ph (**2a**)	45 (**5k**)	87
6	H, Bn (**7g**)	Ph (**2a**)	88 (**5l**)	90
7	H, CH_2CH_2phthalimide (**7h**)	4-BrC_6H_4 (**2b**)	96 (**5q**)	90
8	6-Me, Me (**7i**)	Ph (**2a**)	81 (**5r**)	93

[a] Reaction conditions: 10 mol% (*S*)-**1g**, 0°C, 5 mol% Ru catalyst, 0.05 mol L^{-1} of **7** with 1.5 equiv **2** and activated 4 Å M.S. in toluene at 50°C. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase.

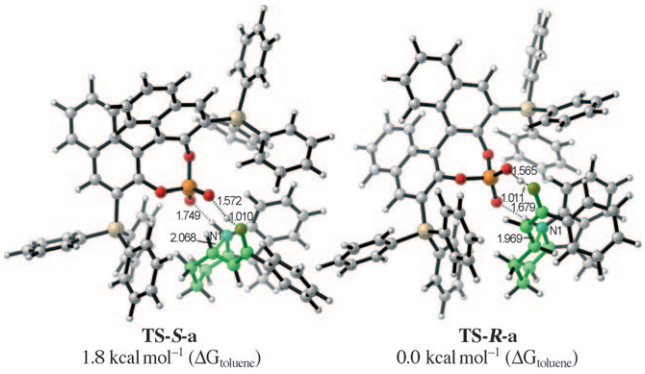
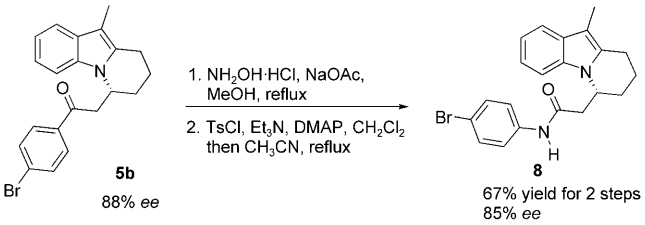
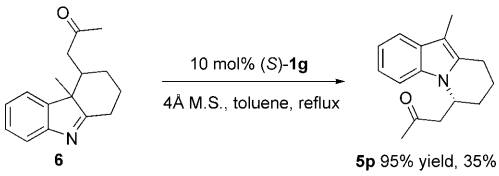


Figure 1. Optimized structures of the two most stable transition states leading to the *S* and *R* products for **5a**, respectively.



Scheme 1. Conversion of ketone **5b** into amide **8**. DMAP = 4-dimethylaminopyridine, Ts = 4-toluenesulfonyl.

[Eq. (6)]. It is likely that the transformation proceeds through a retro-Michael reaction and an aza-Michael addition to afford product **5p**. This experiment suggests that the N1 cyc-



(6)

lization is thermodynamically more favorable. DFT calculations also confirm that the N1 alkylation is both thermodynamically and kinetically favored.[14]

In addition, calculational data on the aza-Michael reaction employing the depicted model system indicate that the transition state corresponding to the *S* product (TS-*S*-a) exhibited stronger steric repulsion between the substrate and one $SiPh_3$ group of the catalyst than that in TS-*R*-a (Figure 1). The calculated free-energy gap between these two transition states is 1.8 kcal mol^{-1}.[14] This prediction was in agreement with the experimental results.[15]

Notably, the enantioenriched aryl ketone product **5b** obtained here could be easily transformed into amide **8** in good yield and without notable loss of optical purity through the Beckmann rearrangement reaction (Scheme 1).

In conclusion, we have developed an enantioselective intramolecular Friedel–Crafts-type aza-Michael addition of an indole catalyzed by a chiral phosphoric acid and excellent product yields and *ee* values were obtained. Furthermore, the combination of organocatalysis and transition-metal catalysis makes the synthesis of these polyheterocyclic structures highly efficient and economical. To our knowlege, this represents the first asymmetric N-alkylation of indoles in the absence of electron-withdrawing groups under acidic reaction conditions. Additional studies on the reaction mechanism are currently underway in the lab.

Experimental Section

General procedure for the asymmetric olefin cross-metathesis/aza-Michael reaction: The indolyl olefin **7** (0.2 mmol), enone **2** (0.3 mmol), and activated 4 Å M.S. (100 mg) were added to toluene (4 mL) in a dry Schlenk tube under an argon atmosphere. The solution was heated to 50°C, and then the chiral phosphoric acid (0.02 mmol) and Ru catalyst (0.01 mmol) were added in one portion. After the reaction was complete (monitored by TLC or ^{1}H NMR analysis), the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:50→1:100) to afford the product.

Received: June 28, 2010
Revised: August 4, 2010
Published online: October 7, 2010

Keywords: asymmetric catalysis · Brønsted acids · heterocycles · Michael addition · synthetic methods

[1] a) J. Bosch, M.-L. Bennasar, *Synlett* **1995**, 587; b) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 4th ed., Blackwell Science, Oxford, **2000**; c) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1; d) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278; e) S.

Agarwal, S. Caemmerer, S. Filali, W. Froehner, J. Knoell, M. P. Krahl, K. R. Reddy, H.-J. Knolker, *Curr. Org. Chem.* **2005**, *9*, 1601; f) S. E. O'Connor, J. J. Maresh, *Nat. Prod. Rep.* **2006**, *23*, 532.

[2] For reviews, see: a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560; *Angew. Chem. Int. Ed.* **2004**, *43*, 550; b) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903; c) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190; d) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; e) M. Zeng, S.-L. You, *Synlett* **2010**, 1289.

[3] For selected examples of asymmetric C3 alkylation of indoles, see: a) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030; b) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; c) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942; d) Y.-Q. Wang, J. Song, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156; e) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 5661; *Angew. Chem. Int. Ed.* **2007**, *46*, 5565; f) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484; g) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, *120*, 603; *Angew. Chem. Int. Ed.* **2008**, *47*, 593; h) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016; i) P. Bachu, T. Akiyama, *Chem. Commun.* **2010**, *46*, 4112.

[4] For selected examples of asymmetric Pictet–Spengler reactions of indoles, see: a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558; b) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086; c) M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2007**, *119*, 7629; *Angew. Chem. Int. Ed.* **2007**, *46*, 7485; d) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404; e) D. J. Mergott, S. J. Zuend, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 745; f) I. T. Raheem, P. S. Thiara, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 1577; g) N. V. Sewgobind, M. J. Wanner, S. Ingemann, R. von Gelder, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2008**, *73*, 6405.

[5] S. Lee, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 15438.

[6] a) D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029; b) Q. Kang, X.-J. Zheng, S.-L. You, *Chem. Eur. J.* **2008**, *14*, 3539; c) M. Zeng, Q. Kang, Q.-L. He, S.-L. You, *Adv. Synth. Catal.* **2008**, *350*, 2169; d) Y.-F. Sheng, G.-Q. Li, Q. Kang, A.-J. Zhang, S.-L. You, *Chem. Eur. J.* **2009**, *15*, 3351; e) L. Hong, C. Liu, W. Sun, L. Wang, K. Wong, R. Wang, *Org. Lett.* **2009**, *11*, 2177; f) L. Hong, W. Sun, C. Liu, L. Wang, K. Wong, R. Wang, *Chem. Eur. J.* **2009**, *15*, 11105.

[7] a) B. M. Trost, M. J. Krische, V. Berl, E. M. Grenzer, *Org. Lett.* **2002**, *4*, 2005; b) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem.* **2008**, *120*, 3282; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238; c) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang, Y.-C. Chen, *Angew. Chem.* **2009**, *121*, 5847; *Angew. Chem. Int. Ed.* **2009**, *48*, 5737; d) L. M. Stanley, J. F. Hartwig, *Angew. Chem.* **2009**, *121*, 7981; *Angew. Chem. Int. Ed.* **2009**, *48*, 7841; e) D. Enders, C. Wang, G. Raabe, *Synthesis* **2009**, 4119; f) L. Hong, W.-S. Sun, C.-X. Liu, L. Wang, R. Wang, *Chem. Eur. J.* **2010**, *16*, 440.

[8] a) E. O. M. Orlemans, W. Verboom, M. W. Scheltinga, D. N. Reinhoudt, P. Lelieveld, H. H. Fiebig, B. R. Winterhalter, J. A. Double, M. C. Bibby, *J. Med. Chem.* **1989**, *32*, 1612; b) D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck, D. Jasserand, *J. Med. Chem.* **1995**, *38*, 669; For a review: c) U. Galm, M. H. Hager, S. G. van Lanen, J. Ju, J. S. Thorson, B. Shen, *Chem. Rev.* **2005**, *105*, 739.

[9] For selected examples under transition-metal catalysis, see: a) M. Kimura, M. Futamata, R. Murai, Y. Tamaru, *J. Am. Chem. Soc.* **2005**, *127*, 4592; b) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; c) N. Kagawa, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2008**, *10*, 2381. For selected examples under organocatalysis, see: d) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482; e) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606.

[10] a) J. J. Vepsalainen, S. Auriola, M. Tukiainen, N. Ropponen, J. Callaway, *J. Planta Med.* **2005**, *71*, 1049; b) R. K. Tiwari, A. K. Verma, A. K. Chhillar, D. Singh, J. Singh, V. K. Sankar, V. Yadav, G. L. Sharma, R. Chandra, *Bioorg. Med. Chem.* **2006**, *14*, 2747; c) R. S. Maciak, PCT Int. Appl. WO2000037022, WO220000629, **2000**; d) M. Ohtani, M. Fuji, M. Adachi, T. Ogawa, PCT Int. Appl. WO22001005789, WO220010152, **2001**.

[11] For reviews, see: a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; b) J. Zhou, *Chem. Asian J.* **2010**, *5*, 422; c) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999.

[12] a) Q. Cai, Z.-A. Zhao, S.-L. You, *Angew. Chem.* **2009**, *121*, 7564; *Angew. Chem. Int. Ed.* **2009**, *48*, 7428; for excellent work on Ru-catalyzed tandem cross-matathesis/intramolecualr hydroatylation sequence, see: b) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu, W.-J. Xiao, *Angew. Chem.* **2008**, *120*, 2523; *Angew. Chem. Int. Ed.* **2008**, *47*, 2489.

[13] Control experiments were carried out to shed light on the high reactivity of the sequential catalysis (see the Supporting Information for details).

[14] See the Supporting Information for details of the DFT calculations.

[15] The absolute configuration was determined by X-ray diffraction analysis of the hydrazone derivatives of **5b**. CCDC 781728□ contains 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.

