Cross-Coupling

DOI: 10.1002/anie.201206346

Tandem Heck/Decarboxylation/Heck Strategy: Protecting-Group-Free Synthesis of Symmetric and Unsymmetric Hydroxylated Stilbenoids**

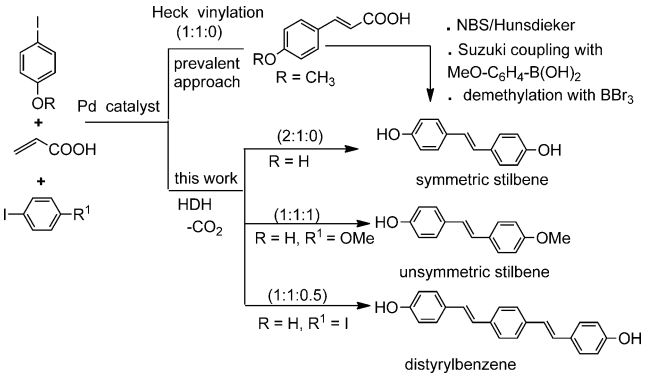
*Amit Shard, Naina Sharma, Richa Bharti, Sumit Dadhwal, Rajesh Kumar, and Arun K. Sinha**

The use of inexpensive[1] raw materials and performing reactions either in a tandem[2] or sequential[3] manner has emerged as an elegant approach in organic synthesis in terms of efficiency, economy, and waste minimization. In this context, the unrivalled diversity of the transition-metal-catalyzed reactions has made them important mediators for the elaboration of tandem processes.[2c]

Notably, palladium-catalyzed Heck coupling[4] between an olefin[4a] and aryl halide (or its surrogates)[4b,c] has garnered significant attention for generating numerous biologically active stilbenoids like resveratrol,[4d] pterostilbene,[4e] etc. However, one of the coupling partners, that is, styrene, is inevitably prone to polymerization, difficult to synthesize, and tricky to purify. To counteract this problem, generation of styrene[5] in situ (by Knoevenagel decarboxylation,[5a–c] Hunsdiecker,[5d] Wittig–Horner,[5e] dehydrohalogenation Heck[5f] reaction) and subsequent tandem coupling with an arylhalide to yield stilbenoids have come to the forefront. In contrast, the synthetic efficiency for hydroxy[6] functionalized stilbenoids is hampered by the involvement of additional protection/deprotection strategies.[6b]

Herein, we describe the palladium-catalyzed tandem Heck/decarboxylation/Heck (HDH) cross-coupling of 4-halophenols with acrylic acid to yield unprecedented symmetric or unsymmetric hydroxylated stilbenoids (C_6-C_2-C_6 unit) or distyrylbenzene (C_6-C_2-C_6-C_2-C_6 unit) in a protecting-group-free manner. The method allows tuning of the concentration of the coupling partners, and CO_2 is the only by-product with respect to the acrylic acid (Scheme 1); conventional coupling of 4-halophenols and acrylic acid are known to provide 4-hydroxy cinnamic acid (C_6-C_3 unit).[7]

Inspired by our recent tandem dehydrative Heck method,[8a] which utilizes in situ generated styrene to construct stilbenoids in ionic liquids (IL),[8] we further envisaged carrying out tandem HDH reactions for the generation of symmetric hydroxylated stilbenoids in neutral ionic liquids.[8a] To accomplish this, coupling of two equivalents of 4-iodophenol (1.83 g, 8.32 mmol) and one equivalent of acrylic acid (0.3 g, 4.16 mmol) was carried out using $Pd(OAc)_2$ (4 mol%), PPh_3 (5 mol%), and piperidine/sodium formate (1.5 equiv each) under microwave (MW) irradiation (120W, 150°C) for 40 minutes in [hmim]Br (1 g), thus providing **1**[5c] in 17% yield (Table 1, entry 1). The [hmim]Br was replaced with *N*,*N*-dimethylacetamide[9] (DMA) and other bases were screened (Table 1, entries 3–11). Piperidine as a base improved the yield of **1** up to 45% (Table 1, entry 8).



Scheme 1. Synthesis of symmetric and unsymmetric hydroxylated stilbenoids and distyrylbenzene by a tandem HDH strategy. The ratios given within parentheses represent the 4-iodophenol/acrylic acid/aryl halide ratio for the reactions.

Further, a detailed optimization study was conducted to evaluate the effect of various solvents, palladium catalysts, and additives (Table 2). Interestingly, use of $[Pd(PPh_3)_4]$ and LiCl as an additive in DMA provided **1** in 52% yield under microwave irradiation (180W, 160°C) after 40 minutes (Table 2, entry 10). In contrast, carrying out the same reaction in an oil bath (160°C) provided **1** in 41% yield (Table 2, entry 13) with a longer reaction time of 360 minutes. Halophenols[10] are a useful class of synthons[10a] and serve as important synthetic handles for the elaboration of numerous organic transformations like the Heck lactonization of 2-halophenols into coumarins[10b] and benzofurans.[10c] However, there is no report on the utilization of their positional variants, such as 4-halophenols, along with acrylic acid for the synthesis of hydroxylated stilbenoids without using a protection/deprotection strategy.[6]

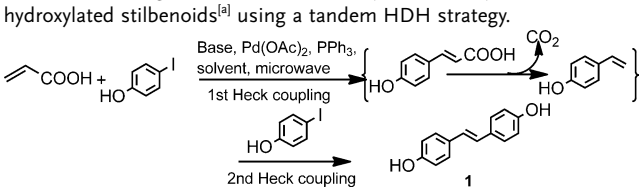
Conventionally, the hydroxy stilbene **1** can be accessed through a protection/deprotection strategy[11] involving Heck coupling between 4-iodoanisole (protected halophenol) and acrylic acid with a subsequent Hunsdiecker reaction[5d,11a]/Suzuki coupling,[11b] and a final demethylation[11c] with boron trihalide. Hence, the utility of our optimized HDH protocol was ascertained through synthesis of a diverse array of

[*] A. Shard, N. Sharma, R. Bharti, S. Dadhwal, R. Kumar, A. K. Sinha
Natural Plant Products Division, C.S.I.R.-Institute of Himalayan Bioresource Technology, Council of Scientific and Industrial Research, Palampur-176061 (H.P.) (India)
E-mail: aksinha08@rediffmail.com

[**] This work was supported by the Council of Scientific and Industrial Research (project MLP 0008 and MLP 0052/ORIGIN). A.S. and R.K. thank the C.S.I.R. for an SRF award. The authors gratefully acknowledge the Director the IHBT, Palampur, for his kind cooperation and encouragement. I.H.B.T. Communication No. 2384.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206346.

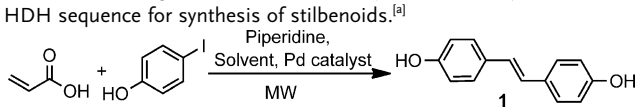
Table 1: Screening of different bases for synthesis of symmetric hydroxylated stilbenoids[a] using a tandem HDH strategy.



Entry	Base	Equiv.	*t* [min]	Yield [%][b]
1	piperidine + HCOONa in IL[c]	1.5 + 1.5	40	17
2	piperidine + K_2CO_3 in IL[c]	1.5 + 1.5	40	25
3	piperidine + K_2CO_3[d]	1.5 + 1.5	40	40
4	HCOONa + K_2CO_3[d]	1.5 + 1.5	40	13
5	K_2CO_3[d]	3	40	11
6	HCOONa[d]	3	40	6
7	KOH[d]	3	40	25
8	piperidine[d]	3	40	45
9	Et_3N[d]	3	40	22
10	Bu_3N[d]	3	40	18
11	DBU[d]	3	40	18

[a] Reaction conditions: 4-iodophenol (8.32 mmol), acrylic acid (4.16 mmol), $Pd(OAc)_2$ (4 mol%), PPh_3 (5 mol%), base, solvent 8 mL, 180 W, 160°C using a CEM monomode microwave. [b] Yield of product isoalted after purification using silica gel column chromatography. [c] [hmim]Br (1-hexyl 3-methyl imidazolium bromide) was used. [d] IL was replaced by DMA in the reactions shown in entries 3–11. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 2: Screening different solvents and palladium catalysts for the HDH sequence for synthesis of stilbenoids.[a]

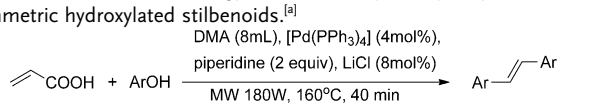


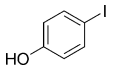
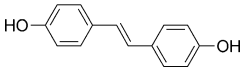
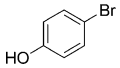
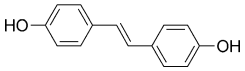
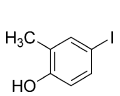
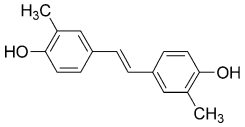
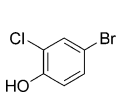
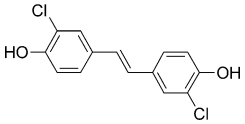
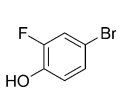
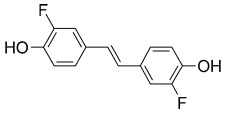
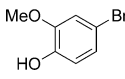
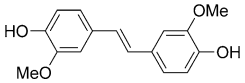
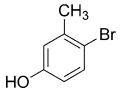
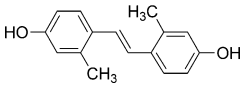
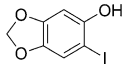
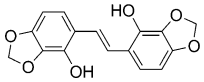
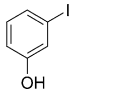
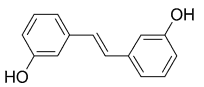
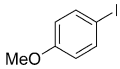
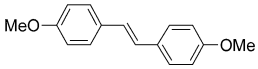
Entry	Solvent	Pd catalyst	Ligand	Additive	Yield[b]
1	DMA	$Pd(OAc)_2$	PPh_3	–	45
2	NMP	$Pd(OAc)_2$	PPh_3	–	21
3	DMF	$Pd(OAc)_2$	PPh_3	–	32
4	PEG 200	$Pd(OAc)_2$	PPh_3	–	24
5	water	$Pd(OAc)_2$	PPh_3	–	22
6	toluene	$Pd(OAc)_2$	PPh_3	–	25
7	DMA	$PdCl_2$	PPh_3	–	20
8	DMA	$Pd(CF_3COO)_2$	PPh_3	–	26
9	DMA	$[Pd(PPh_3)_4]$	–	–	48
10	DMA	$[Pd(PPh_3)_4]$	–	LiCl	52
11	DMA	$[Pd(PPh_3)_4]$	–	Ag_2CO_3	50
12	DMA	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	46
13	DMA	$[Pd(PPh_3)_4]$	–	LiCl	41[c]

[a] Reaction conditions: 4-iodophenol (8.32 mmol), acrylic acid (4.16 mmol), Pd catalyst (4 mol%), ligand (5 mol%), additive (8 mol%), piperidine (3 equiv), 180W, 160°C using a CEM monomode microwave. [b] Yield of isolated product. [c] Conventional heating for 6 h at 160°C. DMF = *N*,*N*′-dimethylformamide, NMP = *N*-methylpyrrolidone, PEG = polyethyleneglycol.

symmetric hydroxylated stilbenoids using acrylic acid and halophenols bearing different substitutents (Table 3, entries 1–7). As expected, coupling of 4-iodophenol and acrylic acid provided **1** (Table 3, entry 1) in good yield relative to the coupling between 4-bromophenol and acrylic acid (entry 2) because 4-iodophenol participates more readily in the Heck reaction[12] (I > Br). It was also observed that 4-

Table 3: Tandem HDH strategy for a three-step, one-pot synthesis of symmetric hydroxylated stilbenoids.[a]



Entry	ArOH	Product		Yield [%][b]
1			**1**	52
2			**1**	41
3			**2**	35
4			**3**	85
5			**4**	76
6			**5**	30
7			**6**	40
8			**7**	n.d.
9			**8**	n.d.
10			**9**	n.d.

[a] Reaction conditions: acrylic acid (4.16 mmol), halophenol (8.32 mmol), $[Pd(PPh_3)_4]$ (4 mol%), LiCl (8 mol%), piperidine (12.44 mmol), DMA (8 mL), 180W, 160°C using a CEM monomode microwave. [b] Yield of isolated product. n.d. = not detected.

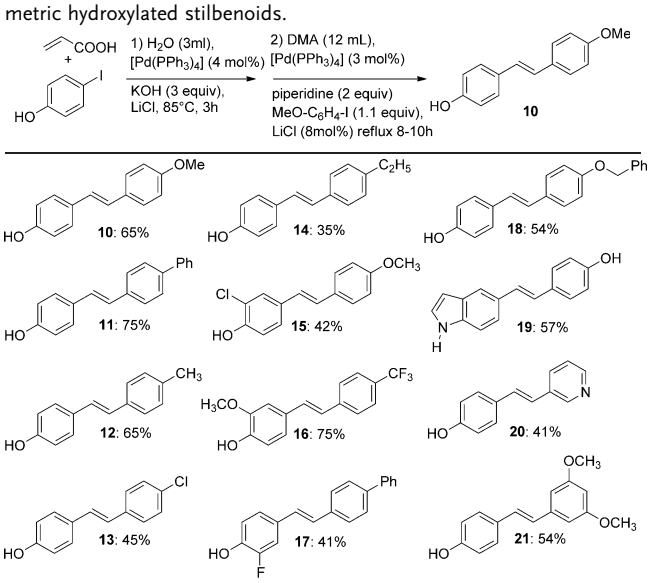
halophenols having electron-withdrawing substituents (Table 3, entries 4 and 5) provided stilbenes in higher yields (up to 85%) relative to the halophenols having electron-donating substituents (entries 3, 6, and 7), which provided stilbenes in moderate yield (up to 40%).This drastic difference in yields may be due to the electron-withdrawing groups facilitating decarboxylation of the intermediate 4-hydroxy cinnamic acid to generate 4-hydroxystyrene (Table 3, entries 4 and 5). Such a discernible difference in yields was also observed by Zhang[13] et al., who reported that cinnamic esters obtained from acrylates and aryl halides were formed in higher yields particularly in the presence of electron-withdrawing substituents. As expected, a 2-halophenol variant of 4-halophenol did not provide **7** because of its poor reactivity towards the Heck coupling/decarboxylation or tendency to form coumarin (Table 3, entry 8).[10b] In a control experiment, reaction of a 3-halophenol or 4-haloanisole (Table 3, entries 9

and 10) with acrylic acid did not lead to the respective stilbenes because they did not undergo the quinomethide[14] mechanism, thus emphatically demonstrating the crucial role played by hydroxy substitution at the *para* position of aromatic ring. Moreover the prerequisite of ethylene gas[15] or the protection/deprotection[16] protocol was altogether avoided for the stilbenoids **1**–**6**.

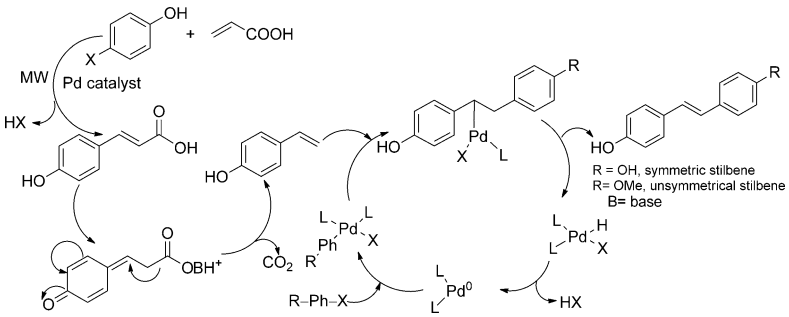
Mechanistically, it is presumed that 4-halophenol reacts with acrylic acid to form 4-hydroxy cinnamic acid (first Heck coupling; Scheme 2) which undergoes decarboxylation according to the quinomethide[5a] mechanism to form 4-hydroxystyrene in situ. The second Heck coupling proceeds with another 4-halophenol to form the symmetric hydroxylated stilbenoid. When 4-haloanisole is used for the second Heck coupling an unsymmetric stilbene results from the HDH protocol.

Now, our goal was to extend the tandem protocol to the synthesis of unsymmetric hydroxylated stilbenoids (see Table 4) which enjoy the status of being privileged motifs in terms of their diverse biological[17] and unambiguous physicochemical[18] profiles. To achieve this, 4-iodophenol, acrylic acid, and 4-iodoanisole were used in 1:1:1 ratio and irradiated

Table 4: One-pot sequential HDH strategy for the synthesis of unsymmetric hydroxylated stilbenoids.



Yields are those of the isolated product.



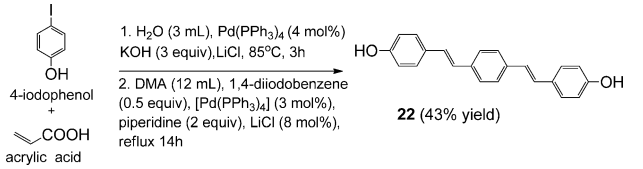
Scheme 2. Plausible mechanism for the synthesis of hydroxylated stilbenoids in one pot.

using a microwave at 160 °C for 40 minutes in DMA (8 mL), and the desired 4-hydroxy-4′-methoxy stilbene (**10**) was furnished in 5 % yield along with the undesired 4-methoxy cinnamic acid (25 % yield), but without formation of the desired intermediate 4-hydroxy cinnamic acid as evidenced by HPLC analysis (see the Supporting information). Additionally, a number of combinations of reaction conditions were applied and conventional heating was preferred presumably because the fast dissipation of energy by MW irradiation[19] could be leading the HDH reaction to favor of the formation of the symmetric stilbene **1** (Table 3) along with cinnamic acid, rather than desired unsymmetric stilbene (**10**). Therefore, the HDH reaction run in sequential one-pot manner to improve the yield of **10** (see the Supporting Information).

Finally, the first Heck coupling between 4-iodophenol (1.0 equiv) and acrylic acid (1.0 equiv) with KOH[20] (3 equiv) in water (3 mL) under conventional heating (85 °C, 3 h) provided the intermediate 4-hydroxy cinnamic acid in 95 % yield (based upon HPLC analysis). But subsequent addition of 4-iodoanisole to the same pot with heating by refluxing (140 °C, 8 h) failed to afford the second Heck coupling product **10** under completely aqueous conditions. It was then decided to use a co-solvent for making the second Heck coupling more facile. Surprisingly, addition of 12 mL DMA[21] (four times the volume of water) and 4-iodoanisole to the same pot with refluxing at 140 °C for 8 hours afforded the desired unsymmetric stilbene **10** in 65 % yield (71 % on HPLC basis) with *E* selectivity by the tandem-sequential HDH strategy (see the Supporting Information).

These optimized reaction conditions were applied to different halophenols, arylhalides, and acrylic acid and successfully provided the unsymmetric stilbenoids **10**–**21** in moderate to good yields (35–75 %). Moreover the methodology provides a concise synthesis of the indole-containing[22] stilbene 4-[(*E*)-2-(1*H*-indol-6-yl)ethenyl]phenol (**19**) and the anticancer natural Pterostilbene[4c] (**21**) in 54 % overall yield (scalable up to 1 gm), whereas a previous multistep protocol[23] provides **21** in 24 % overall yield.

Interestingly, the distyrylbenzene (DSB)[24] (*E*,*E*)-1,4-bis(4-hydroxystryl)benzene (**22**; Scheme 3), possessing wide applications in diagnosis and therapeutics of Alzheimer's



Scheme 3. Tandem sequential synthesis of (*E*,*E*)-1,4- bis(4-hydroxy)-styrylbenzene.

disease,[24b] was also successfully synthesized by the one-pot sequential coupling of halophenol (1.0 equiv) and acrylic acid (1.0 equiv) in the first step to deliver 4-hydroxy cinnamic acid in aqueous medium, and subsequent refluxing with diiodobenzene (0.5 equiv) in the presence of DMA in the second step to afford the hydroxylated DSB in 43% yield by a Heck/decarboxylation/double Heck (HDHH) sequence. This overall yield is in contrast to the reported 16% overall yield.[24c]

In summary, we have for the first time devised a practical tandem/sequential HDH approach for the synthesis of diversely substituted symmetric and unsymmetric hydroxylated stilbenoids and distyrylbenzene. Here, acrylic acid acts as an ethylene surrogate and offers a unique platform for the self-coupling of two molecules of halophenols for the formation of a symmetric stilbene, while cross-coupling of acrylic acid with a halophenol and arylhalide (three coupling partners) provides an unsymmetric stilbene. This diversity oriented construction of hydroxylated stilbenoids offers several advantages such as utilizing readily accessible precursors and it is a protecting-group-free and waste free ($-CO_2$ as by-product) synthesis. The synthesized stilbenoids are amenable to downstream modification as their medicinal and electronic properties can be easily tuned using differently substituted halophenols and aryl halides.

Received: August 7, 2012
Revised: September 9, 2012
Published online: November 5, 2012

Keywords: arenes · cross-coupling · palladium · synthetic methods · tandem reactions

[1] a) S. S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 14194 – 14195; b) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009 – 3066.

[2] a) R. A. Batey, *J. Am. Chem. Soc.* **2007**, *129*, 7476; b) D. I. Chai, M. Lautens, *J. Org. Chem.* **2009**, *74*, 3054 – 3061; c) F. Felpin, O. Ibarguren, L. Nassar-Hardy, E. Fouque, *J. Org. Chem.* **2009**, *74*, 1349 – 1352.

[3] a) J.-P. Leclerc, M. André, K. Fagnou, *J. Org. Chem.* **2006**, *71*, 1711 – 1714; b) S. Yahiaoui, A. Fardost, A. Trejos, M. Larhed, *J. Org. Chem.* **2011**, *76*, 2433 – 2438.

[4] a) M. Oestreich, *The Mizoroki-Heck reaction*, Wiley, Weinheim, **2009**, chap. 1; b) J. Barluenga, C. Valdés, *Angew. Chem.* **2011**, *123*, 7626 – 7640; *Angew. Chem. Int. Ed.* **2011**, *50*, 7486 – 7500; c) A. de Meijere, P. Zezschwitz, H. Nüske, B. Stulgies, *J. Organomet. Chem.* **2002**, *653*, 129 – 140; d) S. M. Nobre, M. N. Muniz, M. Seferin, W. M. da Silva, A. L. Monteiro, *Appl. Organomet. Chem.* **2011**, *25*, 289 – 293; e) J. J. Heynekamp, W. M. Weber, L. A. Hunsaker, A. M. Gonzales, R. A. Orlando, L. M. Deck, D. L. Vander Jagt, *J. Med. Chem.* **2006**, *49*, 7182 – 7189; f) S. F. Zhao, R. X. Zhou, X. M. Zheng, *Indian J. Chem. Sect. A* **2006**, *45A*, 2215 – 2217; g) X.-M. Liu, Y.-C Cui, L. Zhang, X.-W. Zhao, *Yingyong Huaxue* **2006**, *23*, 1286 – 1290; h) Z. Wang, Q. Ding, X. He, J. Wo, *Org. Biomol. Chem.* **2009**, *7*, 863 – 865.

[5] a) N. Sharma, A. Sharma, A. Shard, R. Kumar, Saima, A. K. Sinha, *Chem. Eur. J.* **2011**, *17*, 10350 – 10356; b) A. Sharma, N. Sharma, R. Kumar, A. Shard, A. K. Sinha, *Chem. Commun.* **2010**, *46*, 3283 – 3285; c) A. K. Sinha, R. Kumar, A. Sharma, N. Sharma, WO/2010/113005, **2010**; d) J. P. Das, S. Roy, *J. Org. Chem.* **2002**, *67*, 7861 – 7864; e) J. McNulty, P. Das, *Eur. J. Org. Chem.* **2009**, *2009*, 4031 – 4035; f) A. S. Saiyed, A. V. Bedekar, *Tetrahedron Lett.* **2010**, *51*, 6227 – 6231.

[6] a) C. J. Lion, C. S. Matthews, M. F. G. Stevens, A. D. Westwell, *J. Med. Chem.* **2005**, *48*, 1292 – 1295; b) M. B. Andrus, J. Liu, *Tetrahedron Lett.* **2006**, *47*, 5811 – 5814.

[7] a) N. A. Bumagin, P. G. More, I. P. Beletskaya, *J. Organomet. Chem.* **1989**, *371*, 397 – 401; b) S. Matsuo, Japanese Patent, 2004149438, **2004**; c) S. R. Sheng, Q. Y. Luo, P.-G. Huang, L. Guo, Q. Y. Wang, X. L. Pei, *J. Chem. Res.* **2006**, *2006*, 24 – 26.

[8] a) R. Kumar, A. Shard, R. Bharti, Y. Thopate, A. K. Sinha, *Angew. Chem.* **2012**, *124*, 2690 – 2693; *Angew. Chem. Int. Ed.* **2012**, *51*, 2636 – 2639; b) K. S. A. Vallin, P. Emilsson, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6243 – 6246.

[9] S. Proch, Y. Mei, J. M. R. Villanueva, Y. Lu, A. Karpov, M. Ballauff, R. Kempe, *Adv. Synth. Catal.* **2008**, *350*, 493 – 500.

[10] a) J. Barluenga, A. Jiménez, A. F. Aznar, V. Carlos, *J. Am. Chem. Soc.* **2009**, *131*, 4031 – 4041; b) T. D. A. Fernandes, B. G. Vaz, M. N. Eberlin, A. J. M. Da Silva, P. R. R. Costa, *J. Org. Chem.* **2010**, *75*, 7085 – 7091; c) R. Cano, M. Yus, D. J. Ramon, *Tetrahedron* **2012**, *68*, 1393 – 1400.

[11] a) M. A. Bazin, L. El Kihel, J.-C. Lancelot, S. Rault, *Tetrahedron Lett.* **2007**, *48*, 4347 – 4351; b) C. Kuang, Q. Yang, H. Senboku, M. Tokuda, *Synthesis* **2005**, 1319 – 1325; c) F. A. Khan, S. Choudhury, *Eur. J. Org. Chem.* **2010**, 2954 – 2970.

[12] a) F. Zhao, B. M. Bhanage, M. Shirai, M. Arai, *Chem. Eur. J.* **2000**, *6*, 843 – 848; b) F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771 – 11835.

[13] Z. Zhang, Z. Zha, C. Gan, C. Pan, Y. Zhou, Z. Wang, M.-M. Zhou, *J. Org. Chem.* **2006**, *71*, 4339 – 4342.

[14] A. K. Sinha, A. Sharma, B. P. Joshi, *Tetrahedron* **2007**, *63*, 960 – 965.

[15] T. Jeffery, B. Ferber, *Tetrahedron Lett.* **2003**, *44*, 193 – 197.

[16] I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193 – 205.

[17] a) H. F. Kung, S. R. Choi, W. Qu, W. Zhang, D. Skovronsky, *J. Med. Chem.* **2010**, *53*, 933 – 941; b) Y. Q. Li, Z. L. Li, W. J. Zhao, R. X. Wen, Q. W. Meng, Y. Zeng, *Eur. J. Med. Chem.* **2006**, *41*, 1084 – 1089.

[18] L. Chen, D. W. McBranch, H. L. Wang, R. Helgeson, F. Wudl, D. G. Whitten, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 12287 – 12292.

[19] a) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408 – 6443; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250 – 6284; b) V. P. Mehta, E. V. V. Eycken, *Chem. Soc. Rev.* **2011**, *40*, 4925 – 4936.

[20] A. Ohtaka, T. Yamaguchi, T. Teratani, O. Shimomura, R. Nomura, *Molecules* **2011**, *16*, 9067 – 9076.

[21] a) Q. Yao, E. P. Kinney, C. Zheng, *Org. Lett.* **2004**, *6*, 2997 – 2999; b) C. Nájera, L. Botella, *Tetrahedron* **2005**, *61*, 9688 – 9695.

[22] A. B. S. Maya, C. P. Melero, C. Mateo, D. Alonso, J. L. Fernández, C. Gajate, F. Mollinedo, R. Peláez, E. Caballero, M. Medarde, *J. Med. Chem.* **2005**, *48*, 556 – 568.

[23] M. Roberti, D. Pizzirani, D. Simoni, R. Rondanin, R. Baruchello, C. Bonora, F. Buscemi, S. Grimaudo, M. Tolomeo, *J. Med. Chem.* **2003**, *46*, 3546 – 3554.

[24] a) K. M. Solntsev, P. L. McGrier, C. J. Fahrni, L. M. Tolbert, U. H. F. Bunz, *Org. Lett.* **2008**, *10*, 2429 – 2432; b) D. P. Flaherty, S. M. Walsh, T. kiyota, Y. Dong, T. Ikezu, J. L. Vennerstrom, *J. Med. Chem.* **2007**, *50*, 4986 – 4992; c) S. R. Bayly, E. R. Humphrey, H. D. Chair, C. G. Paredes, Z. R. Bell, J. C. Jeffery, J. A. Claverty, M. D Ward, F. Totti, *J. Chem. Soc. Dalton Trans.* **2001**, 1401 – 1414.

