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Lewis Acid-Catalyzed Conjugate Addition of sp^3 C–H Bonds to Methylenemalononitriles

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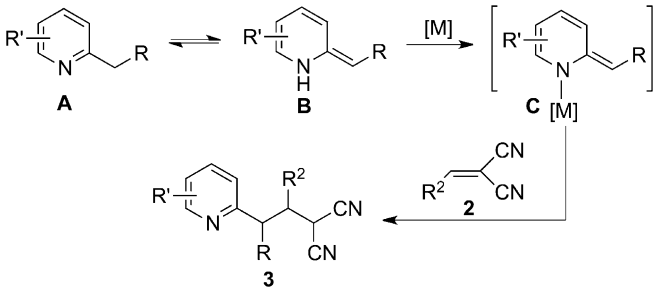
Abstract: The Lewis acid-catalyzed conjugate addition of 2-alkylazaarenes to methylenemalononitriles through sp^3 C–H bond functionalization has been developed, which provides an efficient and reliable method for incorporation of the nitrile group into the heterocycles.

Keywords: 2-alkylazaarenes; conjugate addition; Lewis acids; methylenemalononitriles; sp^3 C–H bonds



Scheme 1. Strategy for the addition of 2-substituted azaarenes to methylenemalononitriles.

Transition metal-catalyzed direct C–H functionalizations have experienced substantial progress and are considered as highly efficient strategies in synthetic organic chemisty for constructing new C–C or C–X (X = N, O) bonds.[1] Among them, the highly atom-efficient direct additions of C–H bonds to carbon-carbon multiple bonds or C=X bonds are extremely promising in synthetic organic chemistry to realize valuable and enviromentally benign organic transformations.[2] Functionalized pyridines and related azaarenes are important heteroarenes that play increasingly important roles in natural compounds synthesis and drug discovery.[3] As a result, a tremendous research effort has been directed to the area of the design of mild, general, and efficient methods for direct C–H functionalization of the pyridine and azaarene cores.[4] The inherent π-electron-deficient nature of pyridine and related azaarene rings results in a low reactivity for the heterocyclic rings, but allows the corresponding benzylic position of the 2-alkyl-substituted azaarenes to act as potentially good carbon nucleophiles due to the fact that the equilibrium between the 2-alkylazaarene **A** and its enamine counterpart **B** could be easily shifted once the acidity of the benzylic proton had been enhanced by a suitable metal catalyst (Scheme 1).[5] Guided by this concept, we recently reported the palladium- and Lewis acid-catalyzed benzylic addition of 2-alkylazaarenes to *N*-sulfonylimines *via* direct sp^3 C–H bond activation, which have been extented by other groups.[6] To further explore the strategy of facile activation of the sp^3 C–H bond, we therefore developed a new conjugate addition reaction *via* C–H functionalization. Herein, we report an efficient Lewis acid-catalyzed conjugate addition of sp^3 C–H bonds to substituted methylenemalononitriles under neutral conditions.[7]

The nitrile moiety is a versatile functional group which can be selectively converted into amines, amides or carboxyl groups under different reaction conditions.[8] Thus, incorporation of nitrile groups into heterocyclic frameworks will be useful in the synthesis of some biologically interesting compounds.[9] Methylenemalononitriles are highly reactive electrophiles and are widely utilized as nitrile group sources for constructing some valuable building blocks *via* catalytic conjugate addition reactions.[10] However, to the best of our knowledge, the direct conjugate addition of the hard nucleophiles (the pK_a of conjugate acids is more than 25)[11] to methylenemalononitriles *via* C–H functionalization under neutral conditions has never been explored. Inspired by our prevoius results and other work,[6] we envisaged that the *in situ* formed active metal enamide species **C** would act as good nu-

Table 1. Optimization of the reaction conditions.[a]

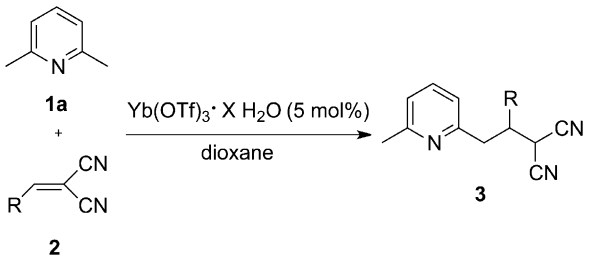
Entry	Catalyst	Solvent	Time [h]	Yield [%][b]
1	$Zn(OTf)_2$	dioxane	18	72
2	$Zn(OTf)_2$	CH_2Cl_2	18	26
3	$Zn(OTf)_2$	MCPE	18	58
4	$Zn(OTf)_2$	$PhCH_3$	18	60
5	$Zn(OTf)_2$	THF	18	57
6	$Zn(OTf)_2$	C_2H_5CN	18	60
7	$Zn(OTf)_2$	DMF	18	70
8	$Zn(OTf)_2$	*i*PrOH	18	62
9	$ZnCl_2$	dioxane	18	48
10	$FeCl_3$	dioxane	18	70
11	$Fe(OAc)_2$	dioxane	18	34
12	$Cu(OTf)_2$	dioxane	18	69
13	$CuBr_2$	dioxane	18	42
14	AgOTf	dioxane	18	52
15	$Sc(OTf)_3$	dioxane	18	71
16	$Pd(OAc)_2$	dioxane	18	36
17	$Y(OTf)_3{\cdot}XH_2O$	dioxane	18	72
18	$Bi(OTf)_3{\cdot}XH_2O$	dioxane	18	75
19	$Eu(OTf)_3{\cdot}XH_2O$	dioxane	18	56
20	$Yb(OTf)_3{\cdot}XH_2O$	dioxane	18	76
21	$Yb(OTf)_3{\cdot}XH_2O$	dioxane	24	82
22	–	dioxane	24	trace

[a] *Reaction conditions:* **1a** (0.75 mmol), **2a** (0.30 mmol), metal catalyst (5 mol%), solvent (1.5 mL), 120 °C for 18–24 h.
[b] Isolated yield.

cleophiles to react with methylenemalononitriles under proper reaction conditions affording the corresponding nitrile functionalized heterocycles (Scheme 1).

To test this possibility, we initiated our study by using 2,6-lutidine **1a** and 2-benzylidenemalononitrile **2a** as substrates for pursuing the optimal conditions for this reaction. A variety of Lewis acids were screened as catalyst on the basis of our previous results. To our delight, in the preliminary trials of using 5 mol% of $Zn(OTf)_2$ as catalyst, the desired conjugate addition reaction proceeded readily at 120 °C in dioxane to give the desired product **3aa** in 72% yield (Table 1, entry 1). Subsequently, a wide range of solvents with different polarity were screened and we found that the reaction performed better in more polar solvents. For example, a 70% yield of **3aa** was attained when DMF was used as solvent, better than that in MCPE (Table 1, entry 3 *vs.* 7). Various Lewis acid catalysts were evaluated in dioxane, which gave the addition product **3aa** in varying yields (Table 1, entries 9–20, 34–76% yields). Different counteranions of the metal can also influence the yields. Metal salts with OTf as conteranion could afford better yields (Table 1, entry 1 *vs.* 9, and 12 *vs.* 13). In view of these results, we selected $Yb(OTf)_3$ which exhibited good catalytic activities in this transformation (Table 1, entry 20, 76% yield) as Lewis acid catalyst for further

Table 2. Substrate scope of methylenemalononitriles.[a]



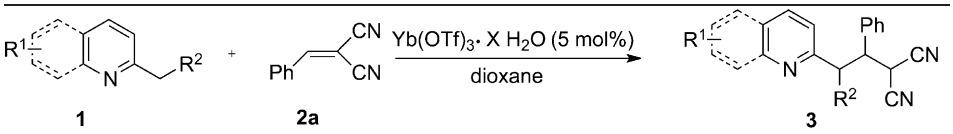
Entry	R	Product	Yield [%][b]
1	C_6H_5	**3aa**	82
2	4-FC_6H_4	**3ab**	99
3	4-ClC_6H_4	**3ac**	90
4	3-ClC_6H_4	**3ad**	96
5	4-BrC_6H_4	**3ae**	89
6	2-BrC_6H_4	**3af**	92
7	2,3-$Cl_2C_6H_3$	**3ag**	96
8	2,4-$Cl_2C_6H_3$	**3ah**	97
9[c]	1-naphthyl	**3ai**	70
10[c]	4-MeC_6H_4	**3aj**	57
11[c]	4-$MeOC_6H_4$	**3ak**	58
12[c]	2-$MeOC_6H_4$	**3al**	66
13[c]	(*E*)-PhCH=CH	**3am**	22
14[c]	*t*-Bu	**3an**	27

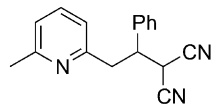
[a] Unless otherwise mentioned, the reaction was performed by using: **1a** (0.75 mmol), **2** (0.30 mmol), $Yb(OTf)_3{\cdot}XH_2O$ (5 mol%), dioxane (1.5 mL), 120 °C for 24 h.
[b] Isolated yield.
[c] 140 °C for 48 h.

exploration. Longer reaction times can afford higher yields of **3aa** (Table 1, entry 21, 82% yield). Thus, the optimized reaction conditions were to use 5 mol% of $Yb(OTf)_3{\cdot}XH_2O$ in dioxane at 120 °C for 24 h. In the absence of catalyst, the desired product **3aa** was not detected (Table 1, entry 22).

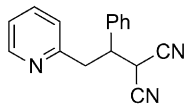
To test the scope of the reaction, a series of substituted methylenemalononitriles were investigated under the optimized conditions. As shown in Table 2, most of the substrates examined here provided the corresponding adduct in good to excellent yields. An array of functionality was tolerated under these conditions including alkyl, ether and halide groups. Obviously, the electronic nature of the substrate **2** has a significant influence on the reactivity for this transformation so that the reaction rate was accelerated by an electron-withdrawing group on the phenyl ring regardless of its *ortho*-, *meta*-, or *para*-position on the aromatic ring (Table 2, entries 2–8, 89–99% yields). Particularly, the 2-(4-fluorobenzylidene)malononitrile **2b** showed outstanding reactivity to give the corresponding product **3ab** in up to 99% yield. 2-(Naphthalen-2-ylmethylene)malononitrile could also be successfully transformed into the desired product **3ai** in 70% yield at 140 °C for 48 h. In contrast, a lower reac-

Table 3. Substrate scope of azaarenes.[a]

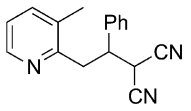




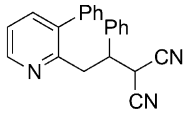
3aa, 82%



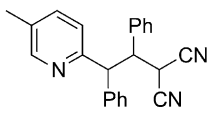
3ba, 48%[b]



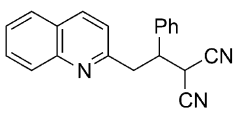
3ca, 59%[a]



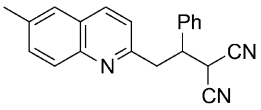
3da, 33%[b]



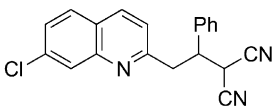
3ea, 53% (1.3:1)[f]



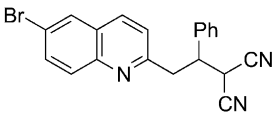
3fa, 69%[c]



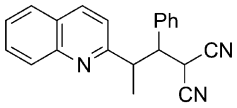
3ga, 79%[d]



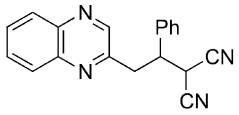
3ha, 70%[d]



3ia, 65%[e]



3ja, 75%[d] (2.4:1)[f]



3ka, 74%

[a] Unless otherwise mentioned, the reaction was performed by using: **1** (0.75 mmol), **2a** (0.30 mmol), $Yb(OTf)_3{\cdot}XH_2O$ (5 mol%), dioxane (1.5 mL), 120 °C for 24 h.
[b] For 36 h.
[c] 80 °C for 24 h.
[d] 120 °C for 3 h.
[e] 120 °C for 12 h.
[f] The *dr* value was determined by ^1H NMR.

tivity was observed in the case of substrates containing an electron-donating group on the phenyl ring of the benzylidenemalononitrile and a higher temperature as well as a longer time were required to get decent yields (Table 2, entries 10–12, 57–66% yields). The cinnamaldehyde- and aliphatic aldehyde-derived methylenemalononitriles (Table 2, entries 13 and 14) were weaker electrophiles than their benzylidenemalononitrile counterparts, giving the corresponding **3am** and **3an** in 22% and 27% yields, respectively, at 140 °C for 48 h.

The scope of the substrate investigation was further extended to a variety of 2-substituted azaarenes. The results are shown in Table 3. To our delight, we found that various substituted 2-methylpyridines could be transformed to the desired products **3aa**–**3ka** in moderate to good yields (33–82% yield). For the 2,3-dimethylpyridine and 2-benzyl-5-methylpyridine, the reactions selectively took place at the 2-benzylic position, respectively, which may due to the higher relative acidity of benzylic protons. This process was also successfully applied to the synthesis of the quinolines and quinoxaline-containing malononitriles, as summarized in Table 3. For these azaarenes, modification of the reaction conditions, including the reaction temperature and reaction time, was required due to the higher reactivity of these azaarenes.[12] Under the modified reaction conditions, the nitrile group could be successfully incorporated into the substituted quinaldines and 2-methylquinoxalines with good yields *via* the Lewis acid-catalyzed C–H addition reactions. Notably, quinaldines and 2-methylquinoxaline could also react with 2-benzylidenemalononitrile **2a** in the absence of Lewis acid catalyst at higher temperature affording the desired addition products in relative lower yields, but higher activity was always observed in the presence of Lewis acid catalyst. These results demonstrated that the Lewis acid indeed played the role of accelerating the reaction process. The struc-

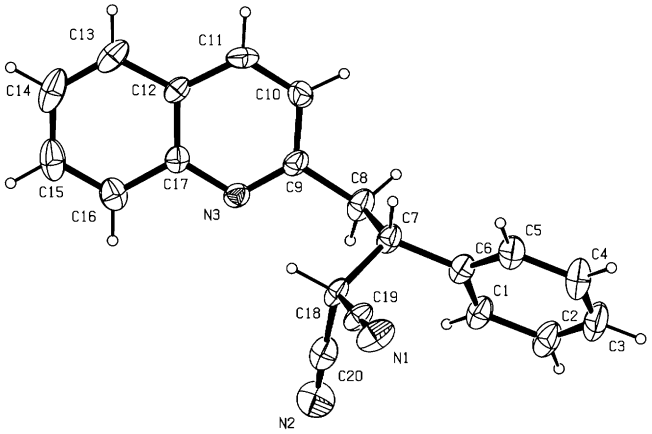


Figure 1. X-ray crystal structure of **3fa**.

ture of these products was further confirmed by X-ray crystallographic analysis of product **3fa** (Figure 1).[13]

In summary, we have successfully developed the direct conjugate addition of 2-alkylazaarenes to methylenemalononitriles to afford heterocycle-containing nitriles *via* C–H bond functionalization. The $Yb(OTf)_3$ was identified as an efficient Lewis acid catalyst for this C–H functionalization reaction. This protocol provides an efficient synthetically useful approach for transformation of azaarenes to valuable medicinal heterocycles.

Experimental Section

Typical Procedure

Under argon, $Yb(OTf)_3{\cdot}XH_2O$ (9.3 mg, 5 mol%), 2,6-lutidine **1a** (0.75 mmol), 2-benzylidenemalononitrile **2a** (0.30 mmol), and dry dioxane (1.5 mL) were added to the screw cap vial. The mixture was kept stirring at 120 °C and monitored by TLC, after 24 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on a silica gel to give the desired product **3aa**.

Acknowledgements

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References

[1] For reviews, see: a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; c) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169; d) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; e) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; f) K. Godula, D. Sames, *Science* **2006**, *312*, 67; g) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041; h) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439; i) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069; j) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; k) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; l) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; m) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; n) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; o) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, 677.

[2] For selected examples: a) Y. Fukumoto, K. Sawada, M. Hagihara, N. Chatani, S. Murai, *Angew. Chem.* **2002**, *114*, 2903; *Angew. Chem. Int. Ed.* **2002**, *41*, 2779; b) Y. Kuninobu, Y. Nishina, C. Nakagawa, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 12376; c) Y. Kuninobu, Y. Nishina, T. Takeuchi, K. Takai, *Angew. Chem.* **2007**, *119*, 6638; *Angew. Chem. Int. Ed.* **2007**, *46*, 6518; d) Y. Kuninobu, Y. Nishina, K. Takai, *Tetrahedron* **2007**, *63*, 8463; e) L. Yang, C. A. Correia, C.-J. Li, *Adv. Synth. Catal.* **2011**, *353*, 2569; f) B.-J. Li, Z.-J. Shi, *Chem. Sci.* **2011**, *2*, 488; g) Y. Li, X.-S. Zhang, K. Chen, K.-H. He, F. Pan, B.-J. Li, Z.-J. Shi, *Org. Lett.* **2012**, *14*, 636; h) J. K. Aydin, J. Szabó, *Org. Lett.* **2008**, *10*, 2881; i) J. Aydin, C. S. Conrad, K. J. Szabó, *Org. Lett.* **2008**, *10*, 5175; j) A. S. Tsai, M. E. Tauchert, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 1248; k) Y. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 2163; *Angew. Chem. Int. Ed.* **2011**, *50*, 2115.

[3] a) A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry*, Elsevier, Oxford, **2008**, Vol. 7; b) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043; c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627.

[4] For selected examples on C–H functionalization of azaarenes, see: a) E. J. Moore, W. R. Pretzer, T. J. O'Connell, J. Harris, L. LaBounty, L. Chou, S. S. Grimmer, *J. Am. Chem. Soc.* **1992**, *114*, 5888; b) M. Murakami, S. Hori, *J. Am. Chem. Soc.* **2003**, *125*, 4720; c) F. Kakiuchi, K. Tsuchiya, M. Matsumoto, E. Mizushima, N. Chatani, *J. Am. Chem. Soc.* **2004**, *126*, 12792; d) K. Godula, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 3648; e) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; f) J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, *129*, 5332; g) A. M. Berman, J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 14926; h) M. Wasa, B. T. Worrel, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 1297; *Angew. Chem. Int. Ed.* **2010**, *49*, 1275; i) P. Guo, J. M. Joo, S. Rakshit, D. Sames, *J. Am. Chem. Soc.* **2011**, *133*, 16338; j) M. Ye, G-L. Gao, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 6964; k) M. Ye, G-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090; l) P. Jochmann, V. Leich, T. P. Spaniol, J. Okuda, *Chem. Eur. J.* **2011**, *17*, 12115.

[5] Similar metal enamides have been reported, see: a) U. Pieper, D. Stalke, *Organometallics* **1993**, *12*, 1201;

b) W.-P. Leung, H. K. Lee, L.-H. Weng, B. S Luo, Z.-Y. Zhou, T. C. W. Mak, *Organometallics* **1996**, *15*, 1785; c) P. C. Andrews, D. R. Armstrong, C. L. Raston, B. A. Roberts, B. W. Skelton, A. H. White, *J. Chem. Soc. Dalton Trans.* **2001**, 996; d) D. Thomas, W. Baumann, A. Spannenberg, R. Kempe, U. Rosenthal, *Organometallics* **1998**, *17*, 2096; e) T. Niwa, H. Yorimitsu, K. Oshima, *Angew. Chem.* **2007**, *119*, 2697; *Angew. Chem. Int. Ed.* **2007**, *46*, 2643.

[6] a) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2010**, *132*, 3650; b) B. Qian, S. Guo, C. Xia, H. Huang, *Adv. Synth. Catal.* **2010**, *352*, 3195; c) B. Qian, P. Xie, Y. Xie, H. Huang, *Org. Lett.* **2011**, *13*, 2580; d) M. Rueping, N. Tolstoluzhsky, *Org. Lett.* **2011**, *13*, 1095; e) H. Komai, T. Yoshino, S. Matsunaga, M. Kanai, *Org. Lett.* **2011**, *13*, 1706.

[7] For selected Lewis acid-catalyzed direct C–H functionalizations, see: a) M. Tobisu, N. Chatani, *Angew. Chem.* **2006**, *118*, 1713; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683; b) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180; c) S. J. Pastine, D. Sames, *Org. Lett.* **2005**, *7*, 5429; d) K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 402; e) P. A. Vadola, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 16525; f) K. M. McQuaid, J. Z. Long, D. Sames, *Org. Lett.* **2009**, *11*, 2792.

[8] a) S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225; b) V. Y. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* **2002**, *102*, 1771; c) T. C. Harrop, P. K. Mascharak, *Acc. Chem. Res.* **2004**, *37*, 253; d) N. Todorovic, E. Awuah, S. Albu, C. Ozimok, A. Capretta, *Org. Lett.* **2011**, *13*, 6180.

[9] a) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 790; b) A. van Loevezijn, J. Venhorst, W. I. Iwema Bakker, C. G. de Korte, W. de Looff, S. Verhoog, J-W. van Wees, M. van Hoeve, R. P. van de Woestijne, M. A. W. van der Neut, A. J. M. Borst, M. J. P. van Dongen, N. M. W. J. de Bruin, H. G. Keizer, C. G. Kruse, *J. Med. Chem.* **2011**, *54*, 7030.

[10] For selected examples: a) M. N. Elinson, S. K. Feducovich, Z. A. Starikova, A. N. Vereshchagin, S. V. Gorbunov, G. I. Nikishin, *Tetrahedron Lett.* **2005**, *46*, 6389; b) X-S. Wang, G-S. Yang, G. Zhao, *Tetrahedron: Asymmetry* **2008**, *19*, 709; c) N. I. Nikishkin, J. Huskens, W. Verboom, *Eur. J. Org. Chem.* **2010**, *35*, 6820; d) K. Takatsu, R. Shintani, T. Hayashi, *Angew. Chem.* **2011**, *123*, 5662; *Angew. Chem. Int. Ed.* **2011**, *50*, 5548; e) S. R. Kolla, Y. R. Lee, *Tetrahedron* **2011**, *67*, 8271; f) H. S. A. Elzahabi, *Eur. J. Med. Chem.* **2011**, *46*, 4025; g) A. S. Girgis, N. S. M. Ismail, H. Farag, *Eur. J. Med. Chem.* **2011**, *46*, 2397.

[11] a) Y. Castanet, F. Petit, *Tetrahedron Lett.* **1979**, 3221; b) E. Keinan, Z. Roth, *J. Org. Chem.* **1983**, *48*, 1769; c) K. H. Shukla, P. DeShong, *J. Org. Chem.* **2008**, *73*, 6283; d) B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc.* **2008**, *130*, 14092.

[12] For quinaldines and 2-methylquinoxaline, the corresponding 2-alkenyl azaarenes were observed when reactions were conducted at a higher temperature for a longer reaction time.

[13] CCDC 875046 (**3fa**) 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.

