EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201300446

The Disubstitution of Acetals to Prepare δ,δ-Bis(aryl) β-Keto Esters

Daniel L. Priebbenow,[a] Liang-Hua Zou,[a] Peter Becker,[a] and Carsten Bolm*[a]

Keywords: Synthetic methods / Arylation / Aromatic substitution / Acetals / Heterocycles / Lewis acids

An efficient catalytic protocol for the synthesis of δ,δ-bis-(aryl)-substituted β-keto esters has been developed. This method involves the Lewis acid catalysed disubstitution reaction of ester-substituted silyl enol ether acetals with a series of aromatic nucleophiles to afford valuable functionalized β-keto esters with several sites available for further derivatisation.

Introduction

Molecules containing two aromatic groups bonded to the same carbon atom have found widespread use in organic chemistry.[1] For example, bis(indolyl)-containing structures (such as **1**, Figure 1) have shown significant bioactivity in a medicinal chemistry setting as peroxisome proliferator-activated receptor γ (PPARγ) agonists, histone deacetylase (HDAC) inhibitors and antimicrobial agents.[2] Furthermore, bis(phenyl) ketones have been prepared as highly active analogues of the commercially available drug modafinil (**2**, Figure 1), currently employed in the treatment of sleep disorders but also showing potential for treating attention deficit hyperactivity disorder (ADHD) and opioid-induced sedation.[3]

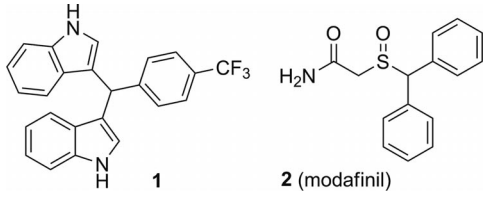
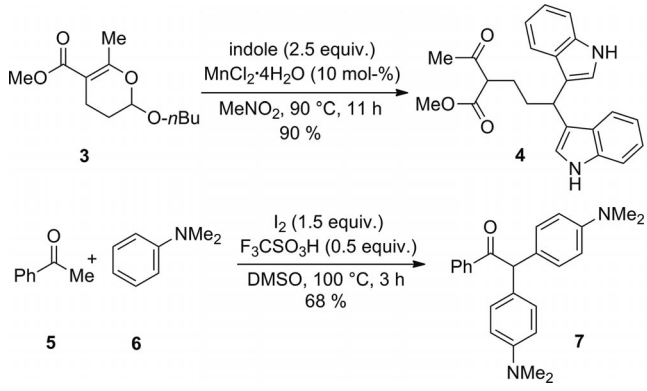


Figure 1. Bioactive molecules containing bis(aryl) functionality.

Several methods have been reported for the incorporation of the bis(aryl) functionality into target molecules. A protocol involving the disubstitution of acetal **3** with indole by employing a manganese catalyst was reported by Gu and co-workers in 2011 (Scheme 1, top).[4] The catalytic disubstitution of aromatic and aliphatic ketones, aldehydes and ethers has also been previously reported by a number of groups.[5] These reactions, presumably involving the formation of an acetal-like intermediate, are facilitated by a catalytic amount of trichloro-1,3,5-triazene[5a] or iodine[5b] in acetonitrile or by using lanthanide triflate catalysts in aqueous methanol or ethanol.[5c,2h] More recently, several palladium-catalysed methods for the preparation of bis(phenyl) ketones from acetophenones and aryl halides have been reported.[6] In addition, a method facilitated by a combination of iodine and trifluoromethanesulfonic acid was used to access bis(phenyl) ketones from acetophenone and electron-rich aromatic nucleophiles (Scheme 1, bottom).[7]



Scheme 1. Recent syntheses of bis(aryl) alkanes and ketones.

The development of new methods to prepare α-bis(aryl) ketones, preferably by utilising mild conditions that do not require high temperatures or expensive transition-metal catalysts, is necessary to allow access to a wider variety of building blocks for organic synthesis and medicinal chemistry. To this end, we herein report a new protocol for the preparation of δ,δ-bis(aryl) substituted β-keto esters from readily accessible enol acetals and electron-rich nucleophilic aromatic species.

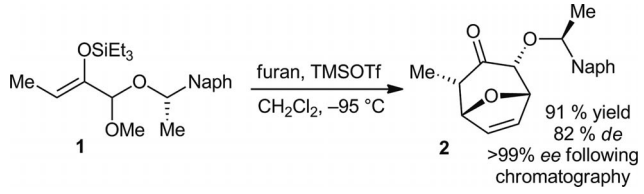
Results and Discussion

Our interest in this area of research began initially with a focus on developing new asymmetric [4+3] cycloaddition methodology. The [4+3] cycloaddition reaction involving

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
E-mail: carsten.bolm@oc.rwth-aachen.de
Homepage: http://bolm.oc.rwth-aachen.de/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300446.

heteroatom-stabilised allyl cations is a reliable and efficient method for the preparation of bridged heterobicyclic scaffolds.[8] In particular, the cycloaddition of oxyallyl cations with suitable dienes provides a very useful class of bicyclo[3.2.1]octene-based compounds that have been subsequently employed in total syntheses of a range of important natural products.[8c,9] To increase the utility of the [4+3] cycloaddition reaction, it is essential that complete diastereo- and enantiocontrol can be achieved during bond formation. However, when compared to other C–C bond-forming processes (including the Diels–Alder reaction), the number of asymmetric [4+3] cycloaddition reactions reported to date remains extremely limited.[10] The few examples of the asymmetric [4+3] cycloaddition that exist involve the use of chiral substrates (see Scheme 2, Naph = naphthyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate),[11] chiral transition-metal complexes,[12] or chiral organocatalysts.[13]

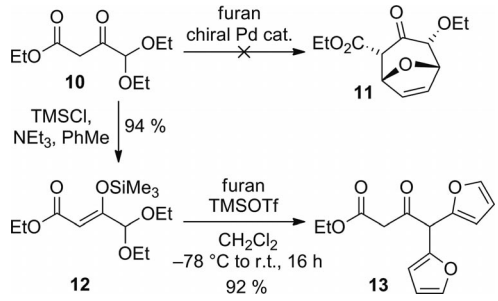


Scheme 2. The asymmetric [4+3] cycloaddition by using a chiral auxiliary.

One method commonly utilised to access the requisite oxyallyl cation for the [4+3] cycloaddition is through the Lewis acid catalysed activation of an enol acetal.[14,8c] In addition, several highly enantioselective transformations of β-keto esters have been recently reported employing dicationic palladium catalysts.[15] As such, to further explore the development of asymmetric [4+3] cycloaddition reactions involving oxyallyl cations, we decided to investigate the use of β-keto ester acetals (such as keto acetal **10**). It was envisaged that such substrates would allow for the utilisation of transition-metal catalysts that could complex the keto ester moiety, which would induce enolisation and provide stereocontrol during activation of the acetal and the ensuing cycloaddition process.

To begin our investigation, β-keto ester acetal substrate **10** was prepared by Claisen condensation of ethyl acetate with ethyl diethoxyacetate in the presence of sodium.[16] Subsequently, a series of chiral dicationic palladium complexes were trialled as catalysts in the proposed cycloaddition reaction between keto acetal **10** and furan (to afford **11**, Scheme 3); however, this substrate failed to undergo the desired [4+3] cycloaddition process.

To allow additional investigations to be carried out, β-keto ester acetal **10** was converted into silyl enol ether **12** by using TMSCl and triethylamine in toluene.[17] In an attempt to first prepare racemic bicyclo[3.2.1]octene **11**, initial reaction attempts of the [4+3] cycloaddition with enol



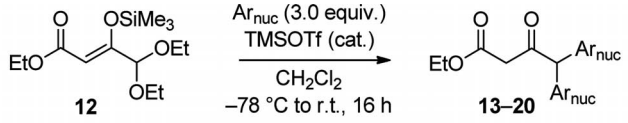
Scheme 3. Attempted [4+3] cycloaddition of β-keto ester acetals.

acetal **12** were performed with furan (5.0 equiv.) and a catalytic amount of TMSOTf in CH_2Cl_2 at –78 °C. Analysis of the reaction mixture following a simple workup after stirring for 16 h revealed that no cycloaddition (to form **11**) had taken place; however, complete conversion of acetal **12** into δ,δ-bis(furan-2-yl) β-keto ester **13** was observed (Scheme 3). Bis(furyl) keto ester **13** was isolated in 92% yield following column chromatography. When the reaction was repeated in the presence of only one equivalent of furan, bis(furyl) keto ester **13** was still the major product formed. Additional studies revealed that the use of alternative solvents and Lewis acids led to much lower levels of conversion to the product. A reduction in the amount of nucleophile employed (to 3.0 equiv.) still afforded high yields of the desired product (Table 1, entry 1).

The scope of the disubstitution of enol acetal **12** was then investigated under the previously optimised reaction conditions by using enol acetal **12** (0.25 mmol) and the aromatic nucleophile (0.75 mmol) in CH_2Cl_2 (3 mL) in the presence of a catalytic amount of TMSOTf. In addition to furan (Table 1, entry 1), a range of nucleophilic aromatic substrates were trialled in this process, and the results are summarised in Table 1. 2-Methylfuran derivative **14** was obtained in 81% yield (Table 1, entry 2). Furthermore, *N*-methylpyrrole performed well in this reaction, as it provided δ,δ-bis(pyrrol-2-yl) β-keto ester **15** in 72% yield (Table 1, entry 3). Activated phenyl substrates such as anisole, 1,3-dimethoxybenzene and 1-methoxynaphthalene also reacted cleanly to afford the corresponding δ,δ-bis(aryl) β-keto esters **16**–**18** (Table 1, entries 4–6). Bis(indol-3-yl) β-keto esters **19** and **20** were prepared using this method by employing indole and *N*-methylindole, respectively (Table 1, entries 7 and 8). Mechanistically, the disubstitution process is proposed to proceed in a stepwise fashion, whereby the monoaromatic substrate is formed, and the monoethoxy-substituted δ-carbon remains electron rich enough for a secondary substitution reaction to form δ,δ-bis(aryl) β-keto esters **13**–**20**.

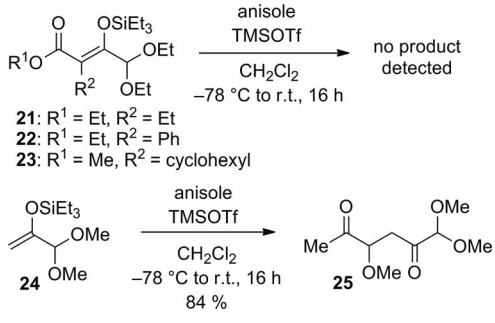
The preparation of more densely functionalised δ,δ-bis(aryl) β-keto esters was then explored by using a series of keto acetals containing α-aliphatic and aromatic functionalities, prepared from Claisen condensation reactions.[18] The β-keto esters were subsequently converted into corresponding silyl enol ethers[11b] **21**–**23** and subjected to the previously identified conditions by employing anisole as the

Table 1. Investigation into the scope of suitable nucleophiles applicable to the disubstitution of enol acetal **12**.



Entry	Nucleophile (Ar_{nuc})	Product (Ar_{nuc} =)	Yield [%]
1	furan	**13**	92
2	2-methylfuran	**14**	81
3	*N*-methylpyrrole	**15**	72
4	anisole	**16**	90
5	1,3-dimethoxybenzene	**17**	88
6	1-methoxynaphthalene	**18**	86
7	indole	**19**	59
8	*N*-methylindole	**20**	87

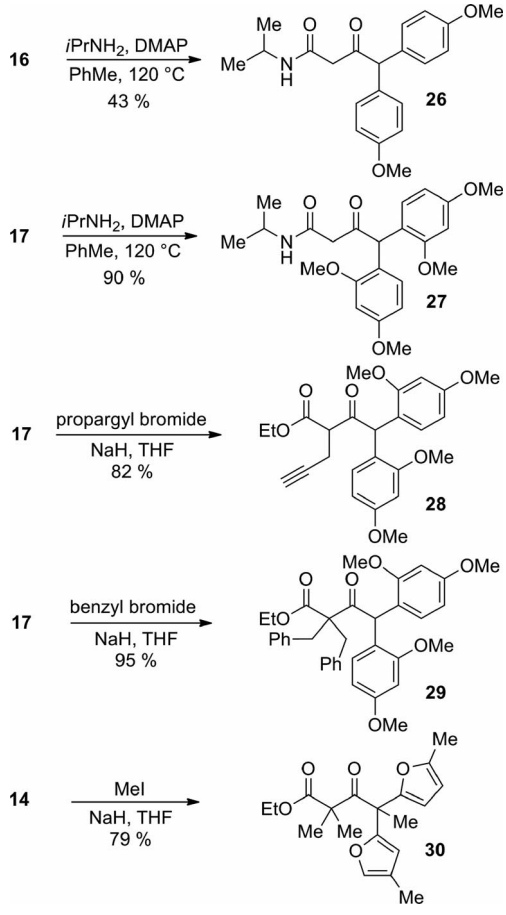
aromatic nucleophile (Scheme 4). In each of these cases, however, the δ,δ-bis(*p*-methoxyphenyl) β-keto esters did not form, and degradation of the starting material was observed.



Scheme 4. Additional attempts to prepare δ,δ-bis(aryl) ketones.

An additional attempt to prepare the δ,δ-bis(*p*-methoxyphenyl) methyl ketone was carried out by using enol acetal **24** and anisole (Scheme 4). Unfortunately, nucleophilic addition of the aromatic nucleophile did not occur, and the major product isolated was diketone **25** in 84% yield, which was formed by dimerisation of enol acetal **24** (Scheme 4).

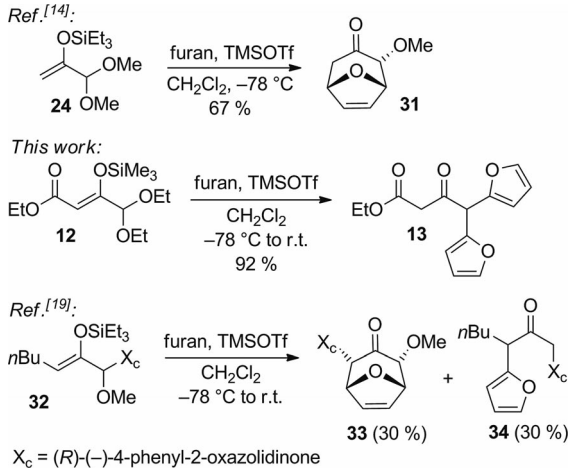
Derivatisation of the δ,δ-bis(aryl) β-keto esters was then explored (Scheme 5). The preparation of modafinil analogues **26** (43% yield) and **27** (90% yield) was readily accomplished through reaction of β-keto esters **16** and **17**, respectively, with isopropylamine.[3] The preparation of more highly substituted bis(aryl) β-keto esters **28**, **29** and **30** could be achieved through reaction with sodium hydride and alkyl halides (Scheme 5). The reaction employing only one equivalent of propargyl bromide provided β-keto ester alkyne **28** in 82% yield (the product was isolated as a 1:1.5 mixture of conformational isomers). A reaction protocol involving two equivalents of benzyl bromide formed dibenzyl β-keto ester **29** in an excellent yield of 95%. In the presence of an excess amount of sodium hydride and methyl iodide, trimethylation of 2-methylfuran derivative **14** afforded β-keto ester **30** in 79% yield.



Scheme 5. Additional derivatisation of the δ,δ-bis(aryl) β-keto esters. DMAP = 4-(dimethylamino)pyridine, DMA = dimethylacetamide.

The investigation reported herein into the potential application of β-keto ester acetals in the [4+3] cycloaddition of oxyallyl cations has further highlighted the role that electronic factors play in the success of the cycloaddition process. If unsubstituted enol acetal **24** is activated by a Lewis

acid in the presence of furan, the cycloaddition proceeds rapidly to afford bicyclo[3.2.1]octene **31** in excellent yield with a high level of diastereoselectivity (Scheme 6).[14] If the enol acetal contains an ester substituent, as in our case, activation of acetal **12** in the presence of furan leads to δ,δ-bis(furan-2-yl) β-keto ester **13** as the sole product through disubstitution in excellent yield. In an analogous example, Hsung and co-workers observed that the use of a chiral aminal instead of the acetal moiety led to the formation of a 1:1 mixture of cycloaddition product **33** and monoaddition product **34** (*dr* ≈ 9:1 for both products in the presence of the chiral auxiliary).[19] As such, to allow further developments to be made in the asymmetric [4+3] cycloaddition reaction, the electronic environment and stability of the requisite oxyallyl cationic species is an important consideration.



Scheme 6. Subtle electronic differences in the enol substrate affect the outcome of the attempted [4+3] cycloaddition.

Conclusions

In summary, an efficient catalytic protocol for the preparation of δ,δ-bis(aryl) β-keto esters has been developed involving the Lewis acid mediated disubstitution of enol acetals. This method proceeded well with a range of aromatic nucleophiles to afford a valuable series of functionalised β-keto esters, which are readily amenable to further derivatisation.

Experimental Section

General Procedure for the Acetal Disubstitution Reaction: To an oven-dried Schlenk tube under an atmosphere of argon was added enol acetal **12** (73 mg, 0.25 mmol), the aromatic nucleophile (0.75 mmol) and CH_2Cl_2 (3 mL). After cooling of this solution to –78 °C, a few drops of TMSOTf were added. The reaction mixture was stirred at this temperature for 2 h and then warmed to room temperature and stirred for an additional 14 h. After this time, the solvent was evaporated, and the product was purified by column chromatography (pentane/ethyl acetate) to afford the bis(aryl) β-keto ester product.

Supporting Information (see footnote on the first page of this article): Detailed description of the experimental procedures and analytical data for all compounds.

Acknowledgments

In part, this research was supported by the Cluster of Excellence (Tailor-Made Fuels from Biomass) funded by the Excellence Initiative of the German Federal and State Governments. The authors acknowledge the Alexander von Humboldt Foundation for a postdoctoral fellowship to D. L. P. and the Chinese Scholarship Council (CSC) for a predoctoral stipend to L. H. Z.

[1] For selected recent examples, see: a) A. Mallick, U. K. Roy, B. Haldar, S. Pratihar, *Analyst* **2012**, *137*, 1247; b) P. Kaur, S. Kaur, K. Singh, P. R. Sharmac, T. Kaurc, *Dalton Trans.* **2011**, *40*, 10818; c) K. Vanderlaag, Y. Su, A. E. Frankel, R. C. Burghardt, R. Barhoumi, G. Chadalapaka, I. Jutooru, S. Safe, *BMC Cancer* **2010**, *10*, 669; d) J. Lukstaitea, D. Gudeikaa, J. V. Grazuleviciusa, S. Grigaleviciusa, B. Zhangb, Z. Xieb, *React. Funct. Polym.* **2010**, *70*, 572; e) S.-X. Cai, D.-H. Li, T.-J. Zhu, F.-P. Wang, X. Xiao, Q.-Q. Gu, *Helv. Chim. Acta* **2010**, *93*, 791; f) H. S. Patela, D. J. Patela, *Int. J. Polym. Mater.* **2010**, *59*, 307.

[2] a) A. Kamal, M. Naseer, A. Khan, K. S. Reddy, Y. V. V. Srikanth, S. K. Ahmed, K. P. Kumar, U. S. N. Murthy, *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 559; b) G. Sivaprasad, P. T. Perumal, V. R. Prabavathy, N. Mathivanan, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6302; c) C. Pisano, P. Kollar, M. Gianni, Y. Kalac, V. Giordano, F. F. Ferrara, R. Tancredi, A. Devoto, A. Rinaldi, A. Rambaldi, S. Penco, M. Marzi, G. Moretti, L. Vesci, O. Tinti, P. Carminati, M. Terao, E. Garattini, *Blood* **2002**, *100*, 3719; d) B. S. Sasidhar, J. S. Biradar, *Med. Chem. Res.* **2012**, DOI: 10.1007/s00044-012-0370-x; e) M. Shankar, A. Balasubramaniam, N. L. Gowrishankar, S. Mahendran, *Pharm. Chem. J.* **2012**, *46*, 381; f) C. Qin, D. Morrow, J. Stewart, K. Spencer, W. Porter, R. Smith, T. Phillips, M. Abdelrahim, I. Samudio, S. Safe, *Mol. Cancer Ther.* **2004**, *3*, 247; g) C. Praveen, P. DheenKumar, D. Muralidharan, P. T. Perumal, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7292; h) G. Giannini, M. Marzi, M. Di Marzo, G. Battistuzzi, R. Pezzi, T. Brunetti, W. Cabri, L. Vesci, C. Pisano, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2840.

[3] C. De Risi, L. Ferraro, G. P. Pollini, S. Tanganelli, F. Valente, A. C. Veronese, *Bioorg. Med. Chem.* **2008**, *16*, 9904 and references cited therein.

[4] M. Li, J. Yang, Y. Gu, *Adv. Synth. Catal.* **2011**, *353*, 1551.

[5] a) G. V. M. Sharma, J. J. Reddy, P. S. Lakshmi, P. R. Krishna, *Tetrahedron Lett.* **2004**, *45*, 7729; b) B. P. Bandgar, K. A. Shaikh, *Tetrahedron Lett.* **2003**, *44*, 1959; c) D. Chen, L. Yu, P. G. Wang, *Tetrahedron Lett.* **1996**, *37*, 4467; d) ; G. Giannini, M. Marzi, G. P. Moretti, S. Penco, M. O. Tinti, S. Pesci, F. Lazzaro, F. De Angelis, *Eur. J. Org. Chem.* **2004**, 2411; e) X. Guo, S. Pan, J. Liu, Z. Li, *J. Org. Chem.* **2009**, *74*, 8848; f) Y.-P. Zhu, M.-C. Liu, F.-C. Jia, J.-J. Yuan, Q.-H. Gao, M. Lian, A.-X. Wu, *Org. Lett.* **2012**, *14*, 3392; g) H.-M. Dong, H.-H. Lu, L.-Q. Lu, C.-B. Chen, W.-J. Xiao, *Adv. Synth. Catal.* **2007**, *349*, 1597; h) J. S. Yadav, B. V. S. Reddy, G. Satheesh, A. Prabhakarb, A. C. Kunwar, *Tetrahedron Lett.* **2003**, *44*, 2221; i) T. P. Pathak, J. G. Osiak, R. M. Vaden, B. E. Welm, M. S. Sigman, *Tetrahedron* **2012**, *68*, 5203.

[6] a) A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209; b) F. Churruca, R. SanMartin, I. Tellitu, E. Dominguez, *Tetrahedron Lett.* **2003**, *44*, 5925; c) F. Churruca, R. SanMartin, I. Tellitu, E. Dominguez, *Org. Lett.* **2002**, *4*, 1591; d) G. A. Grasa, T. J. Colacot, *Org. Lett.* **2007**, *9*, 5489; e) J. R. Schmink, N. E. Leadbeater, *Org. Lett.* **2009**, *11*, 2575.

[7] Y.-P. Zhu, F.-C. Jia, M.-C. Liu, L.-M. Wu, Q. Cai, Y. Gao, A.-X. Wu, *Org. Lett.* **2012**, *14*, 5378.

[8] a) M. Harmata, *Chem. Commun.* **2010**, *46*, 8886; b) M. Harmata, *Chem. Commun.* **2010**, *46*, 8904; c) I. V. Hartung, H. M. R. Hoffmann, *Angew. Chem.* **2004**, *116*, 1968; *Angew. Chem. Int. Ed.* **2004**, *43*, 1934; d) I. Fernandez, J. L. Mascarenas, *Org. Biomol. Chem.* **2012**, *10*, 699; e) A. G. Lohse, R. P. Hsung, *Chem. Eur. J.* **2011**, *17*, 3812.
[9] a) M. Presset, Y. Coquerel, J. Rodriguez, *Chem. Rev.* **2013**, *113*, 525; b) T. Sumiya, K. Ishigami, H. Watanabe, *Angew. Chem.* **2010**, *122*, 5659; *Angew. Chem. Int. Ed.* **2010**, *49*, 5527; c) J. Xu, E. J. E. Caro-Diaz, A. Batova, S. D. E. Sullivan, E. A. Theodorakis, *Chem. Asian J.* **2012**, *7*, 1052; d) A. M. Misske, H. M. R. Hoffmann, *Chem. Eur. J.* **2000**, *6*, 3313; e) Y. Lian, L. C. Miller, S. Born, R. Sarpong, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 12422; f) A. M. Misske, H. M. R. Hoffmann, *Tetrahedron* **1999**, *55*, 4315.
[10] M. Harmata, *Adv. Synth. Catal.* **2006**, *348*, 2297, and references cited therein.
[11] For selected recent examples, see: a) C. B. W. Stark, U. Eggert, H. M. R. Hoffmann, *Angew. Chem.* **1998**, *110*, 1337; *Angew. Chem. Int. Ed.* **1998**, *37*, 1266; b) C. B. W. Stark, S. Pierau, R. Wartchow, H. M. R. Hoffmann, *Chem. Eur. J.* **2000**, *6*, 684; c) B. Lo, S. Lam, W.-T. Wong, P. Chiu, *Angew. Chem.* **2012**, *124*, 12286; *Angew. Chem. Int. Ed.* **2012**, *51*, 12120; d) E. H. Krenske, K. N. Houk, A. G. Lohse, J. E. Antoline, R. P. Hsung, *Chem. Sci.* **2010**, *1*, 387; e) W. K. Chung, S. K. Lam, B. Lo, L. L. Liu, W.-T. Wong, P. Chiu, *J. Am. Chem. Soc.* **2009**, *131*, 4556; f) J. E. Antoline, E. H. Krenske, A. G. Lohse, K. N. Houk, R. P. Hsung, *J. Am. Chem. Soc.* **2011**, *133*, 14443; g) H. Beck, C. B. W. Stark, H. M. R. Hoffmann, *Org. Lett.* **2000**, *2*, 883.
[12] J. Huang, R. P. Hsung, *J. Am. Chem. Soc.* **2005**, *127*, 50.
[13] M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058.
[14] D. H. Murray, K. F. Albizati, *Tetrahedron Lett.* **1990**, *31*, 4109.
[15] a) Y. Hamashima, D. Hotta, N. Umebayashi, Y. Tsuchiya, T. Suzuki, M. Sodeoka, *Adv. Synth. Catal.* **2005**, *347*, 1576; b) N. Umebayashi, Y. Hamashima, D. Hashizume, M. Sodeoka, *Angew. Chem.* **2008**, *120*, 4264; *Angew. Chem. Int. Ed.* **2008**, *47*, 4196; c) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240.
[16] C. M. Alder, I. R. Baldwin, N. P. Barton, A. J. Campbell, A. C. Champigny, J. D. Harling, A. C. Maxwell, J. K. Simpson, I. E. D. Smith, C. J. Tame, C. Wilson, J. M. Woolven (Glaxo Group Limited, GlaxoSmithKline), *Pyrimidine Derivatives used as ITK Inhibitors*, International Patent Number WO 2010/106016 A1, Sept. **2010**.
[17] P. Langer, T. Eckardt, *Synlett* **2000**, 844.
[18] A. Schäfer, A. Wellner, R. Gust, *ChemMedChem* **2011**, *6*, 794.
[19] H. Xiong, R. P. Hsung, L. Shen, J. M. Hahn, *Tetrahedron Lett.* **2002**, *43*, 4449.

Received: March 26, 2013
Published Online: May 13, 2013

