Natural Products Synthesis

DOI: 10.1002/anie.201303893

# Total Syntheses of (±)-Spiroquinazoline, (−)-Alantryphenone, (+)-Lapatin A, and (−)-Quinadoline B**

*Mingyao Wu and Dawei Ma**

Since (−)-spiroquinazoline (**1**; Figure 1) was isolated by Barrow and Sun in 1994,[1] eight other spiroquinazoline alkaloids have been isolated from a variety of fungi of the genera *Penicillium* and *Aspergillus*.[2] These natural products all contain a tricyclic pyrazino quinazolinedione moiety, but differ in the substructures which bridge C2 and C11. (−)-Spiroquinazoline (**1**), (−)-alantryphenone (**2**),[2d] alantryleunone (**3**),[2d] alanditrypinone (**4**),[2d] (+)-lapatin A (**5**),[2c] and (−)-quinadoline B (**9**)[2e] are bridged by indoline-containing substructures with different C15 substituents, while lapatin B (**6**),[2c] alantrypinone (**7**),[2b] and serantrypinone (**8**)[2a] are bridged by a 3-methyleneoxindole unit. Preliminary studies have revealed that these alkaloids possessed significant biological activities. For example, **1** inhibits substance P (SP) binding to human NK-1 receptor and therefore may serve as a lead compound for developing analgesics.[1] Alantrypinone (**7**) potently inhibits insect GABA receptors but is much less active toward mammalian GABA receptors.[2a] Additionally, **9** was found to inhibit lipid droplet synthesis in mouse macrophages.[2e]

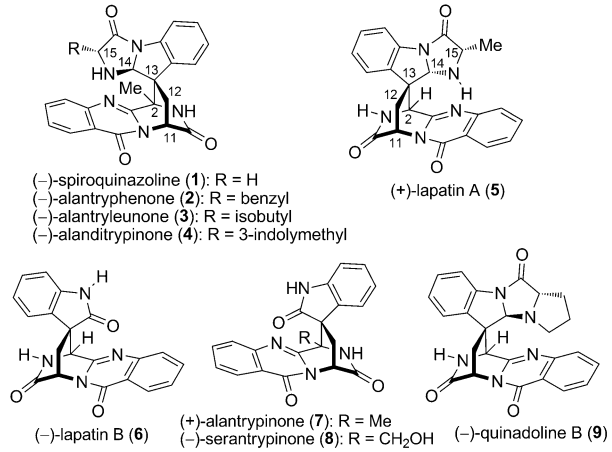



***Figure 1.*** Structures of spiroquinazoline alkaloids.

Since **1** has a skeleton unprecedented in nature, it is not surprising that synthetic interest in this target and related alkaloids has been considerable.[3] To date, several synthetic routes to the core of **1** and total syntheses of two oxindole-containing spiroquinazoline alkaloids have been published,[4] however, the indoline-containing spiroquinazoline alkaloids have not, as yet, succumbed to synthesis.[5] Herein, we wish to report the first total syntheses of (±)-spiroquinazoline (**1**), (−)-alantryphenone (**2**), (+)-lapatin A (**5**), and (−)-quinadoline B (**9**).

A key challenge to the total synthesis of the indoline-containing spiroquinazoline alkaloids is the installation of their aminal moieties. Indeed, despite successful model studies, Hart and Magomedov described that they could not construct the aminal unit in **1** from two alantrypinone derivatives (**10**; Figure 2).[3,5b] Their result implied that formation of the aminal part at an early stage in the synthesis of **1** is necessary. In synthesis of **7**, reported by Kende et al., an aza-Diels–Alder reaction of the azadiene **14** with 3-methyleneoxindole was employed to construct its carbon framework.[4c,d] Inspired by their results, we decided to explore the possibility to utilize the olefins **11**–**13** as the dienophiles for similar transformations. The success of this cycloaddition would provide quick access to indoline-containing spiroquinazoline alkaloids. However, this remained a challenging task at the outset because the stability of these unprecedented

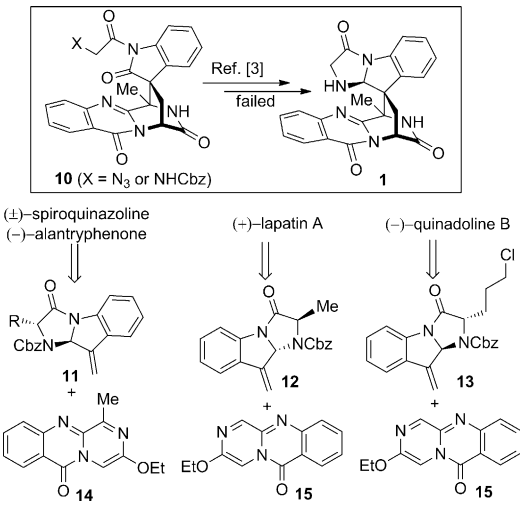
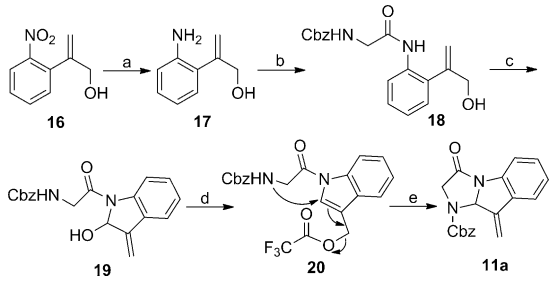



***Figure 2.*** Retrosynthetic analysis of spiroquinazoline alkaloids. Cbz = benzyloxycarbonyl.

[*] M. Wu, Prof. Dr. D. Ma
State Key Laboratory of Bioorganic & Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (P.R. China)
E-mail: madw@mail.sioc.ac.cn

[**] The authors are grateful to the National Basic Research Program of China (973 Program, grant 2010CB833200), the Chinese Academy of Sciences, and the National Natural Science Foundation of China (grant 21132008 & 20921091) for their financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201303893.



***Scheme 1.*** Reagents and conditions: a) Fe, AcOH, 88%; b) EDCI, *N*-Cbz-glycine, $Et_3N$, $CH_2Cl_2$, 82%; c) Dess–Martin periodinane, 95%; d) $CF_3CO_2H$, $CHCl_3$; e) PhBr, 160°C, 50% yield for two steps.

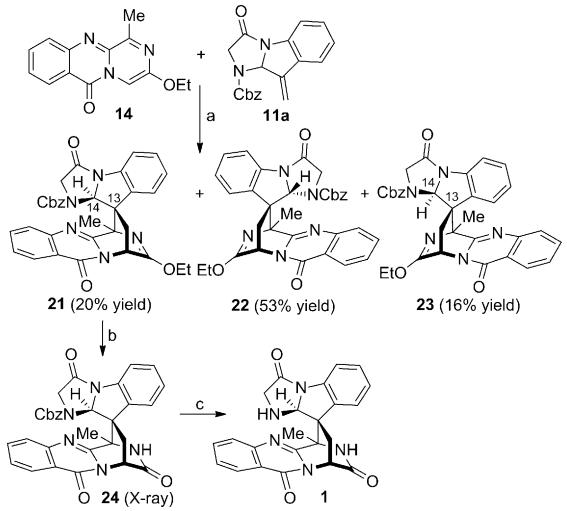
olefins was hitherto unknown, and their reactivity in an aza-Diels–Alder reaction[6] with **14** and **15**[7] was questionable.

As depicted in Scheme 1, the preparation of the olefin **11a** began with the Fe/HOAc reduction of **16**, a known compound which was prepared from commercially available 2-nitrophenylacetic acid in three steps.[8] The resultant aniline **17** was condensed with *N*-Cbz-glycine to afford the amide **18**. Dess–Martin oxidation of **18** with concomitant intramolecular condensation provided the cyclic hemiaminal **19**. Our initial studies focused on obtaining **11a** directly from **19** by treatment with suitable acids because similar transformations have been reported.[5b,9] Unfortunately, exposure of **19** to TsOH or $Sc(OTf)_3$ gave complex mixtures, presumably because the resultant N acyliminium is rather unstable under these reaction conditions. Occasionally, we found that the indole **20** could be isolated in 58% yield when **19** was treated with 1 equivalent of TFA. We envisioned that this side product could be converted into **11a** by a concerted nucleophilic addition-elimination process, and therefore attempted to improve the reaction yield. Gratifyingly, when 12 equivalents of TFA was added, **20** could be obtained in 95% yield. After some experimentation, we found that heating **20** at 160°C in bromobenzene could deliver **11a**. Fortunately, **11a** was stable during long-term storage at room temperature, although it underwent complete decomposition after few days in $CDCl_3$.

With the olefin **11a** in hand, we next investigated its aza-Diels–Alder reaction with the azadiene **14** (Scheme 2). After some optimization, we were pleased that heating a mixture of **11a** and **14** in xylene at 130°C afforded the desired adduct **21** in 20% yield, together with its two isomers, **22** and **23**. Their structures were determined by NMR analysis and further confirmed by subsequent studies. Interestingly, regiochemistry in the adducts **21**–**23**, as well as the preferred *exo*like stereochemistry (displayed by **21** and **22**), are consistent with those observed in the cycloaddition of **14** and 3-methyleneoxindole,[4c,d] although the C–C double bond in **11a** is much less polar than that of 3-methyleneoxindole. Further mechanism investigations are required to rationalize these results.

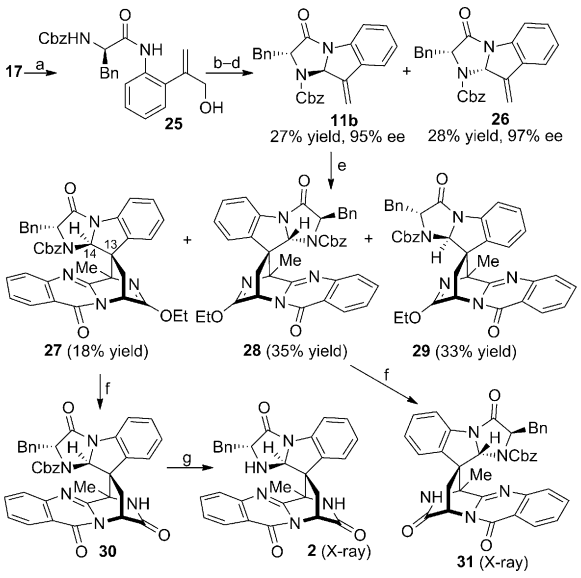
Hydrolysis of **21** with hydrochloride acid in EtOAc produced the lactam **24**, whose structure was confirmed by X-ray analysis.[10] Finally, hydrogenolysis of **24** furnished **1**.[11]

In view of this encouraging result, we next explored if this strategy could be extended to the synthesis of other indoline-containing spiroquinazolines. Accordingly, condensation of **17** with *N*-Cbz-D-phenylalanine provided the amide **25**



***Scheme 2.*** Reagents and conditions: a) xylene, 130°C, 3 days; b) HCl, EtOAc, 95%; c) Pd/C, $H_2$, EtOAc, 80%.

(Scheme 3). By using a procedure similar to the one for preparation of **11a**, **25** was transformed into **11b** and its diastereomer **26**. To our delight, both **11b** and **26** retained satisfactory enantiopurity, thus indicating that almost no



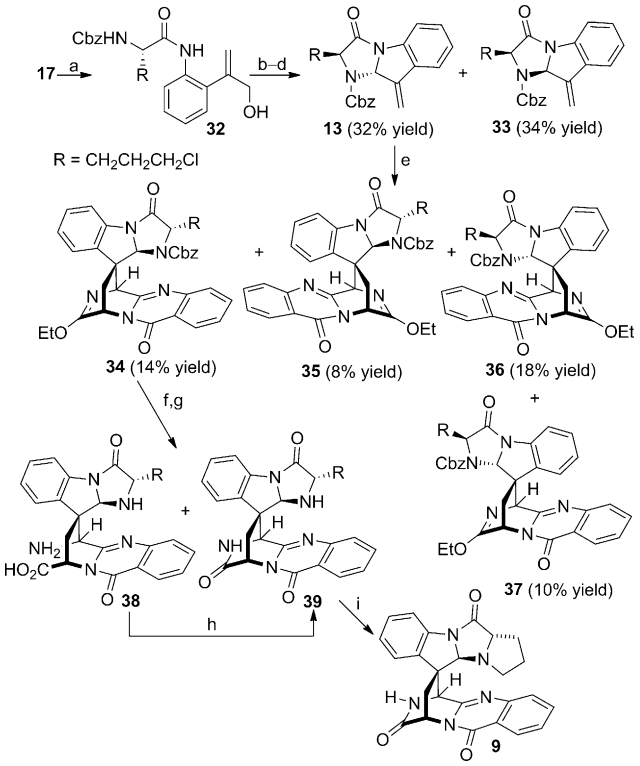
***Scheme 3.*** Reagents and conditions: a) EDCI, *N*-Cbz-D-phenylalanine, $Et_3N$, $CH_2Cl_2$, 76%; b) Dess–Martin periodinane; c) $CF_3CO_2H$, $CHCl_3$; d) PhBr, 160°C; e) **14**, xylene, 130°C, 2 days; f) HCl, THF, 91–94%; g) Pd/C, $H_2$, THF, 86%. EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide, THF = tetrahydrofuran.

racemization occurred during their synthesis. The aza-Diels–Alder reaction of **11b** and **14** took place under our previous reaction conditions, thus providing **27**–**29** in a combined yield of 88%. Hydrolysis of **27** and subsequent hydrogenolysis of the resultant **30** delivered **2** ($[\alpha]_D^{20} = -40$ ($c = 0.017$, MeOH); lit.[2d] $[\alpha]_D^{20} = -1.6$ ($c = 0.9$, MeOH)).[12] In a parallel procedure, **28** was hydrolyzed to lactam **31**. The structures for both the

synthetic **2** and **31** was confirmed by X-ray analysis,[10] thereby allowing us to confirm the structures of the adducts **27** and **28**.

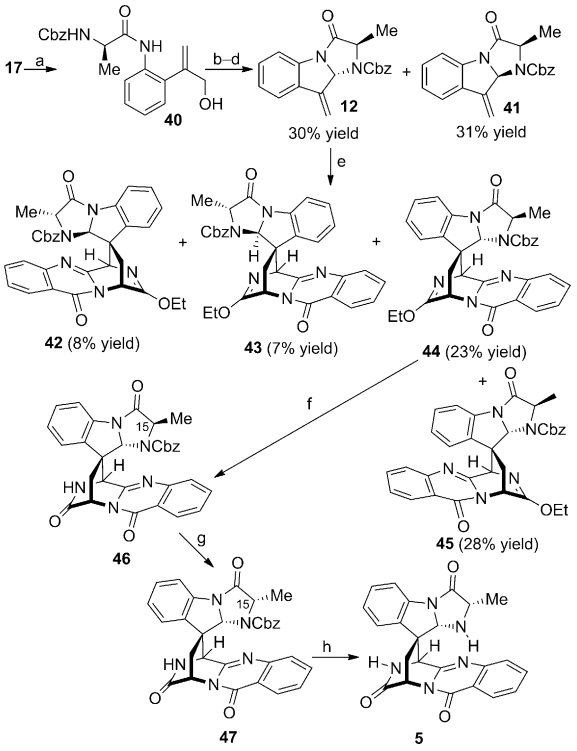
For the synthesis of (−)-quinadoline B (**9**), we condensed the aniline **17** with 2-(*S*)-(benzyloxycarbonylamino)-5-chloropentanoic acid[13] to afford the amide **32** (Scheme 4), which was converted into the desired olefin **13** in three steps and 32% overall yield. Cycloaddition of **13** with **15** produced the




***Scheme 4.*** Reagents and conditions: a) EDCI, 2-(*S*)-(benzyloxy-carbonylamino)-5-chloropentanoic acid, $Et_3N$, $CH_2Cl_2$, 76%; b) Dess–Martin periodinane; c) $CF_3CO_2H$, $CHCl_3$; d) PhBr, 160°C; e) **15**, xylene, 130°C, 48 h; f) Pd/C, $H_2$, THF, MeOH, 90%; g) HCl, THF; h) toluene, reflux; i) $iPr_2NEt$, KI, MeCN, reflux, 40% for three steps.

adducts **34**–**37** in 50% combined yield. Notably, four stereoisomers are simultaneously formed in this case. These results illustrated that the substituents in azadienes have a significant influence on the stereochemical course. Next, deprotection of the expected isomer **34** provided a mixture of **39** and the ring-opened product **38**. The latter could be converted into **39** by refluxing in toluene.[14] Finally, treatment of **39** with $iPr_2NEt$/KI to form the pyrrolidine ring[15] afforded **9** ($[\alpha]_D^{20} = -52.7$ ($c = 0.1$, MeOH); lit.[2e] $[\alpha]_D^{20} = -44.7$ ($c = 0.01$, MeOH)). To our satisfaction, all $^1H$ NMR and $^{13}C$ NMR spectroscopic data for synthetic **9** correlated well with those reported for natural (−)-quinadoline B.

As shown in Scheme 5, we employed a slightly different route to achieve the total synthesis of (+)-lapatin A (**5**). After condensation of **17** with *N*-Cbz-D-alanine to give the amide **40**, our standard four-step conversion was conducted to yield the olefins **12** and **41**. Cycloaddition of **12** and **15** furnished the adducts **42**–**45**. Since **44** has the required stereochemistry for assembling **5**, except for its configuration at the C15




***Scheme 5.*** Reagents and conditions: a) EDCI, *N*-Cbz-D-alanine, $Et_3N$, $CH_2Cl_2$, 81%; b) Dess–Martin periodinane; c) $CF_3CO_2H$, $CH_2Cl_2$; d) PhBr, 160°C, 4 h; e) **15**, xylene, 130°C, 48 h; f) HCl, THF, 90%; g) DBU, DMSO, 110°C, 73%; h) Pd/C, $H_2$, MeOH, 83%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethylsulfoxide.

stereocenter, we decided to use this intermediate for further transformation and planned to fix the C15 stereochemistry problem by epimerization at a late stage.[16] Accordingly, hydrolysis of **44** afforded the lactam **46**, which was treated with DBU in DMSO at 110°C to give a mixture of **46** and the desired isomer **47** in a ratio of 1:3.5. This mixture could be purified by column chromatography to give **47** in 73% yield. After hydrogenolysis of **47**, **5** ($[\alpha]_D^{20} = +41.3$ ($c = 0.09$, EtOH); lit.[2c] $[\alpha]_D^{20} = +22$ ($c = 0.01$, EtOH)) was isolated in 83% yield, and the analytical data are identical with those reported for natural (+)-lapatin A.

In conclusion, we have achieved the first total syntheses of four indoline-containing spiroquinazoline alkaloids, namely (±)-spiroquinazoline, (−)-alantryphenone, (+)-lapatin A, and (−)-quinadoline B. These syntheses each required only 11 to 12 steps from commercially available 2-nitrophenylacetic acid, and the key elements include formation of aminal-embodied olefins and their aza-Diels–Alder reaction with the azadienes. Our synthetic routes provide a quick access to indoline-containing spiroquinazoline alkaloids and their analogues, which will be of benefit for further evaluation of their biological activity. In addition, it is notable that aminal-embodied olefins we obtained are valuable building blocks for synthesizing other aminal-embodied alkaloids. Detailed mechanistic studies to the aza-Diels–Alder reaction, as well as attempts to improve stereoselectivity in this step, are actively being pursued in our group and the results will be disclosed in due course.

Received: May 7, 2013
Revised: June 17, 2013
Published online: July 19, 2013

**Keywords:** cycloaddition · heterocycles · natural products · structure elucidation · synthetic methods

[1] a) C. J. Barrow, H. H. Sun, *J. Nat. Prod.* **1994**, *57*, 471.
[2] a) T. O. Larsen, K. Frydenvang, J. C. Frisvad, C. Christophersen, *J. Nat. Prod.* **1998**, *61*, 1154; b) M. R. Ariza, T. O. Larsen, B. O. Peterson, J. Ø. Duus, C. Christophersen, A. F. Barrero, *J. Nat. Prod.* **2001**, *64*, 1590; c) T. O. Larsen, B. O. Petersen, J. Ø. Duss, D. Sørensen, J. C. Frisvad, M. E. Hansen, *J. Nat. Prod.* **2005**, *68*, 871; d) F. A. Proença Barros, E. Rodrigues-Filho, *Biochem. Syst. Ecol.* **2005**, *33*, 257; e) N. Koyama, Y. Inoue, M. Sekine, Y. Hayakawa, H. Homma, S. Omura, H. Tomoda, *Org. Lett.* **2009**, *10*, 5273.
[3] D. J. Hart, *ARKIVOC* **2010**, *4*, 32.
[4] a) D. J. Hart, N. Magomedov, *Tetrahedron Lett.* **1999**, *40*, 5429; b) D. J. Hart, N. Magomedov, *J. Am. Chem. Soc.* **2001**, *123*, 5892; c) A. S. Kende, J. Fan, Z. Chen, *Org. Lett.* **2003**, *5*, 3205; d) Z. Chen, J. Fan, A. S. Kende, *J. Org. Chem.* **2004**, *69*, 79; e) D. J. Hart, G. Oba, *Tetrahedron Lett.* **2007**, *48*, 7069; f) S. J. Walker, D. J. Hart, *Tetrahedron Lett.* **2007**, *48*, 6218.
[5] a) D. J. Hart, N. A. Magomedov, *J. Org. Chem.* **1999**, *64*, 2990; b) A. Yomadis, O. Barbosa, D. J. Hart, N. A. Magomedov, *Tetrahedron* **2006**, *62*, 8748; c) S. Chen, R. M. Williams, *Tetrahedron* **2006**, *62*, 11572.
[6] a) E. N. Morris, E. K. Nenninger, R. D. Pike, J. R. Scheerer, *Org. Lett.* **2011**, *13*, 4430; b) K. A. Margrey, A. J. Chinn, S. W. Laws, R. D. Pike, J. R. Scheerer, *Org. Lett.* **2012**, *14*, 2098; c) S. Jin, P. Wessig, J. Liebscher, *J. Org. Chem.* **2001**, *66*, 3984; d) J. F. Sanz-Cervera, R. M. Williams, J. A. Marco, J. M. López-Sánchez, F. González, M. E. Martíneza, F. Sancenón, *Tetrahedron* **2000**, *56*, 6345.
[7] a) T. Watanabe, M. Arisawa, A. Nishida, K. Narusuye, M. S. Alam, Y. Ozoe, K. Yamamoto, M. Mitomi, *Bioorg. Med. Chem.* **2009**, *17*, 94; b) D. Leca, F. Gaggini, J. Cassayre, O. Loiseleur, S. N. Pieniazek, J. A. R. Luft, K. N. Houk, *J. Org. Chem.* **2007**, *72*, 4284.
[8] Y. Yasui, H. Kamisaki, T. Ishida, Y. Takemoto, *Tetrahedron* **2010**, *66*, 1980.
[9] a) S. Kozo, S. Eiki, K. Hironori, H. Kou, F. Keiichiro, K. Tetsuji, *J. Org. Chem.* **1986**, *51*, 3007; b) J. P. Scovill, J. H. Burckhalter, *J. Heterocycl. Chem.* **1980**, *17*, 23; c) Y. S. Lee, S. H. Kim, S. H. Jung, S. J. Lee, H. Park, *Heterocycles* **1994**, *37*, 303; d) N. Gigant, E. Claveau, P. Bouyssou, I. Gillaizeau, *Org. Lett.* **2012**, *14*, 844.
[10] CCDC 937851 (**24**), 937852 (**2**), and 937853 (**31**) contain 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.
[11] There are some slight differences between the $^{1}$H NMR and $^{13}$C NMR data we measured for synthetic **1** and those reported for natural (±)-spiroquinazoline (see the Supporting Information), and might result from the difference in the conditions under which the measurements were taken.
[12] Besides rotation differences, we also found some differences between $^{13}$C NMR data we measured for synthetic **2** and those reported for natural (−)-alantryphenone. However, the $^{1}$H NMR data of synthetic **2** are in agreement with those reported for natural (−)-alantryphenone (see the Supporting Information).
[13] J. E. Baldwin, R. M. Adlington, C. R. A. Godfrey, V. K. Patel, *Tetrahedron* **1993**, *49*, 7837.
[14] E. M. Stocking, J. F. Sanz-Cervera, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 1675.
[15] W. Zi, D. Ma, *Angew. Chem.* **2010**, *122*, 6023; *Angew. Chem. Int. Ed.* **2010**, *49*, 5887.
[16] a) T. H. Graham, C. M. Jones, N. T. Jui, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 16494; b) R. A. Lazarus, *J. Org. Chem.* **1990**, *55*, 4755.