C–H Activation

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Copper-Catalyzed Regioselective Intramolecular Oxidative α-Functionalization of Tertiary Amines: An Efficient Synthesis of Dihydro-1,3-Oxazines**

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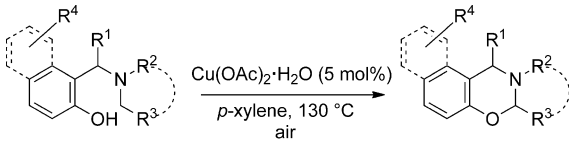
Oxidative coupling reactions, especially through cross-dehydrogenative coupling (CDC) of C–H bonds, which avoids the prefunctionalization of substrates, have recently been in focus for being more atom economical, directive, and environmentally benign than other cross-coupling reactions.[1] Among the CDC reactions, the functionalization of sp^3 C–H bonds adjacent to a nitrogen atom has generally been achieved utilizing transition metal catalysts with co-oxidants, such as *tert*-butylhydroperoxide (TBHP), H_2O_2, molecular oxygen, and others, to generate iminium ion species, which in turn react with various nucleophiles.[2] For this purpose, metals such as Ru,[3] Fe,[4] Rh,[5] V,[6] and others are often used. However, copper salts retain many advantages, such as ready availability, low cost, high efficiency and low toxicity, and have turned out to be the most efficient catalysts for the α-functionalization of tertiary amines.[7] More recently, homogeneous copper catalysis have also been used to achieve the selective aerobic oxidative functionalization of C–H bonds.[8] However, such copper-catalyzed functionalization, whether under aerobic or anaerobic conditions, is mainly confined to the benzylic position of *N*-phenyltetrahydroisoquinoline. Examples relating to the activation of non-benzylic methyl/methylene C–H, are scarce.[9] Hence, despite significant development in recent years, still more research in this area is required to enhance the selectivity and substrate scope. Looking for synthetic advances in regiocontrolled C–H functionalization, we became interested in the design of a synthetic strategy for a copper-catalyzed aerobic oxidative/dehydrogenative α-functionalization of tertiary amines with subsequent intramolecular sp^3 C–O bond formation.

Dihydro-1,3-oxazine derivatives are important heterocyclic molecules, which exhibit a wide range of pharmacological activity, including antibacterial,[10] fungicidal,[11] antitumor,[12] antituberculosis,[13] and anti-HIV.[14] Naphthoxazine derivatives have therapeutic potential for the treatment of Parkinson's disease, and are also used as potent nonsteroidal progesterone receptor agonists.[15] They can be used as intermediates in the synthesis of *N*-substituted aminoalcohols, bioactive natural products, or in asymmetric catalysis.[16] Justifiably, the intrinsic versatility and synthetic utility of these heterocyclic systems has attracted great interest from chemists, who have developed several exquisite methods for their synthesis.[17] However, except for a few examples,[18] most of the reported strategies are primarily based on Mannich type condensations, which are restricted to the use of aliphatic alicyclic primary amines. Hence, regardless of these advances, investigations in search of more efficient routes for the synthesis of these compounds are still highly desirable for drug discovery and medicinal chemistry. Herein, we disclose an efficient, environmentally friendly, diastereoselective copper-catalyzed synthesis of naphtho and benzo-2,3-dihydro-1,3-oxazines through regioselective C–H bond activation and cyclization (Scheme 1).



Scheme 1. Synthesis of 2,3-dihydro-1,3-oxazines.

Because of the importance of naphthoxazine derivatives, we chose the transformation of **1a** into **2a** as a model for optimizing the reaction conditions. Different solvents and metal catalysts, with or without additives, were screened, and $Cu(OAc)_2 \cdot H_2O$ (5 mol%) in *p*-xylene at 130°C were determined to be the optimized conditions (Supporting Information, Table SA). Among the two types of sp^3 C–H bonds

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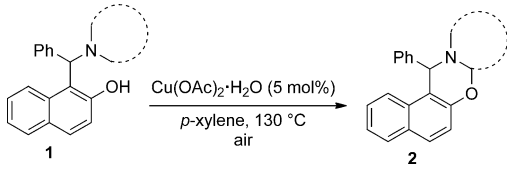
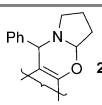
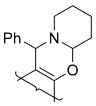
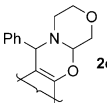
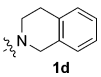
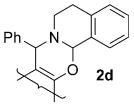
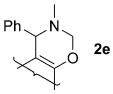
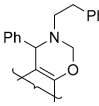
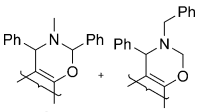
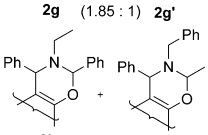
adjacent to the nitrogen atom, α-functionalization occurred mainly at the non-benzylic position, forming 2,3-dihydro-1,3-oxazine **2a**. We also obtained the corresponding ketone **3a** in up to 15% yield as a by-product, depending upon the oxidizing agent used (Table SA). After optimization, a variety of derivatives of aminonaphthol were screened (Table 1). The procedure proved nonetheless to be sensitive to the nature of secondary amines used for the preparation of aminonaphthol/phenol derivatives **1**. As expected, compounds derived from benzylic amines were found to be most reactive and to produce the corresponding oxazines in better yields (Table 1, entries 4 and 8). Upon changing the amine moiety from pyrrolidine to piperidine, the yield of the corresponding product decreased by a small extent (entries 1 and 2). The yield of product was further reduced in the presence of a morpholine group (entry 3) and the inactivity of the piperazine derivative signified that the extra heteroatom, having a readily available lone pair, might interact with Cu ion, resulting in the retardation of α-functionalization. A primary C–H bond adjacent to the nitrogen atom was regioselectively activated relative to the secondary one (entry 6), whereas the benzylic C–H reacted more readily than non-benzylic primary and secondary C–H bonds (entries 7 and 8). Most significantly, single diastereomers of the desired naphtho-1,3-oxazines were obtained.

Table 1: Screening of tertiary amines for the synthesis of 2,3-dihydro-1,3-naphthoxazines.[a]



1 2

Entry	Aminonaphthol	*t* [h]	Product[b]	Yield [%][c]
1	 1a	2	 2a	85
2	 1b	4	 2b	67
3	 1c	7	 2c	58
4	 1d	2	 2d	91
5	 1e	4	 2e	58
6	 1f	3	 2f	66
7	 1g	3	 2g (1.85 : 1) 2g'	70
8	 1h	3	 2h (3 : 1) 2h'	81

[a] Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), *p*-xylene (1 mL) at 130°C. [b] Only the *trans* isomer was obtained, as determined by NMR spectroscopy. [c] Products were purified by preparative TLC; yields shown are of isolated products.

Secondary amine derivative **4** produced binaphthol **5** instead of the desired 1,3-oxazine (Scheme S2). When subjected to these reaction conditions, indoline derivative **6** exclusively produced the corresponding indole **7** (Scheme S3).

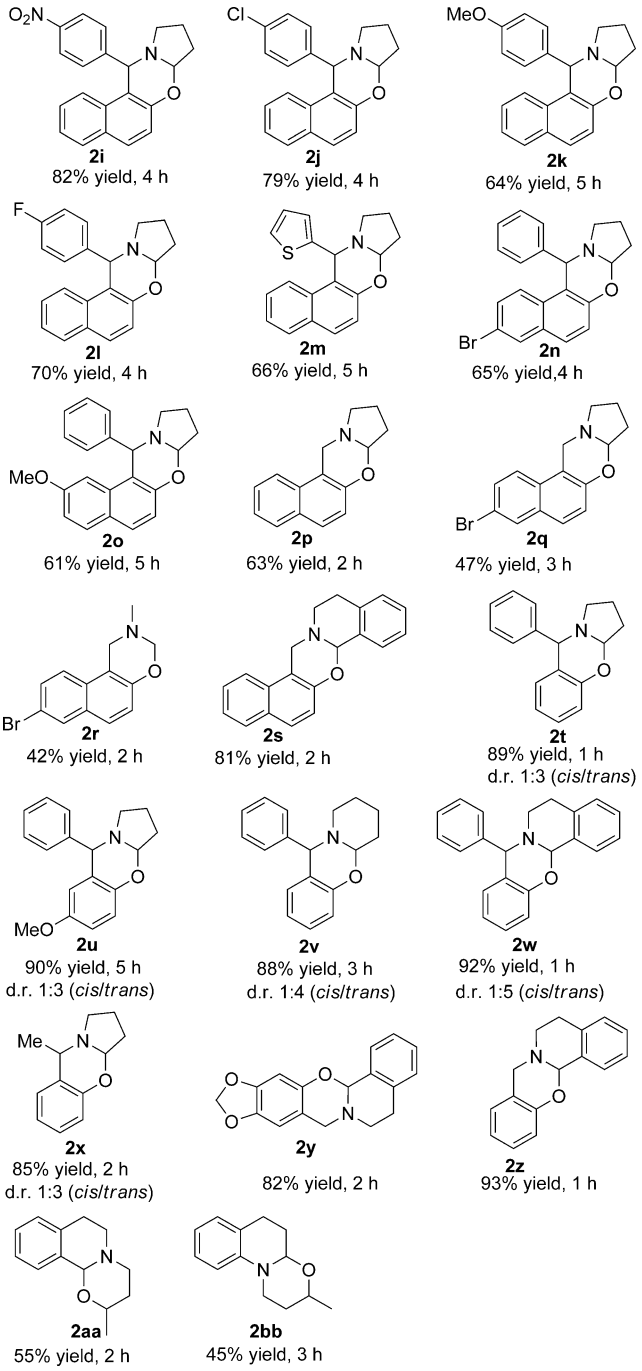
To examine the efficiency and generality of this method, various substituted tertiary aminonaphthols/phenols were investigated under the optimized conditions, as summarized in Scheme 2. The corresponding dihydro-1,3-oxazines, which contain a wide range of substituents, could be obtained in moderate to excellent yields. To our delight, functional groups on the aromatic ring such as OMe, Br, F, Cl, and NO_2 were also compatible. The substrate bearing a thiophene heterocyclic moiety underwent a facile oxidative coupling to furnish the expected product **2m** in good yield. The diastereoselectivity appeared to be particularly sensitive to the substrate chosen: it decreased drastically when exchanging the naphthyl moiety for a phenyl group. Remarkably, the regioselectivity of the α-functionalization of the tertiary amine was not severely affected by switching the nature of the benzylic carbon from a methanetriyl group (**2a** and **2v**) to a methanediyl group (**2p** and **2z**). Hence, the existence of possible steric hindrance arising from the presence of a substituent at the benzylic position was not the only reason for the regioselectivity (cyclization vs. ketone/aldehyde formation). This fact also highlighted the directing nature of the phenolic OH group in the reaction.

To ascertain the role of copper ions in such a regioselective C–H functionalization, in hope of an intermolecular C–O bond formation, a reaction was performed with substrate **8** and phenol **9** under the reaction conditions described in Table 1. Unfortunately, only benzaldehyde **10** and tetrahydroisoquinoline **11** were formed, presumably through iminium ion formation by direct activation of the exocyclic benzylic methylene group (Scheme S4).

The above results indicated that the chelation of copper ions with the nitrogen and the phenolic OH group in a conformationally rigid system (**1a**–**z**), directed dehydrogenative oxidation to take place at the carbon in close proximity to the phenolic OH group.

To obtain further information about the mechanism of the reaction, a cross experiment was performed under the optimized conditions using a 1:1 mixture of **1b** and **1i.** The two expected products (**2b** and **2i**) were isolated along with two cross products (**2a** and **2ib**) in a ratio of 1.5:1.5:1:1, respectively (Scheme 3).

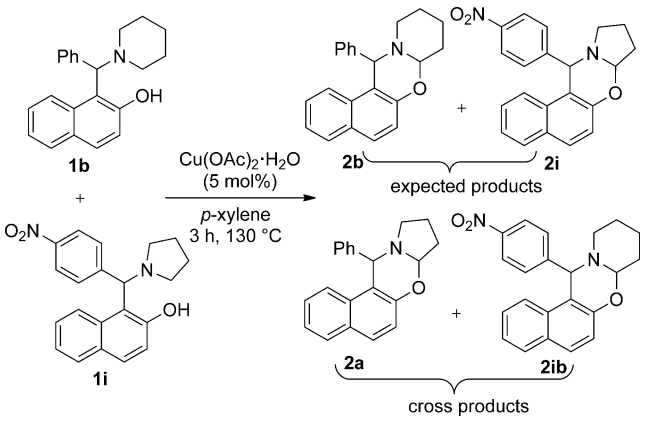
Under the same conditions, the enantiomerically pure starting material **1a′**[19] gave the partially racemized product **2a′** (Scheme 4).[20] These two experiments implied the detach-



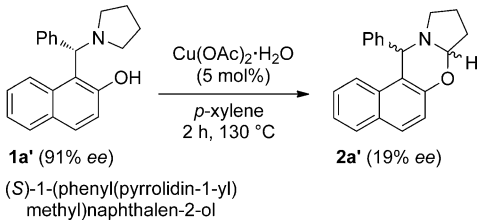
Scheme 2. Substrate scope for the synthesis of 1,3-oxazines. Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), *p*-xylene (1 mL) at 130°C. Yields shown are of isolated products. Isomer ratios are not specified where only the *trans* isomer was observed by NMR spectroscopy.

ment of the pyrrolidine moiety from **1** with the formation of an oxabutadiene intermediate (*o*-quinone methide) during the course of the reaction.

When our model reaction was carried out in degassed *p*-xylene under a continuous flow of argon, **1a** remained almost intact; even after 4 h, only traces of product **2a** were obtained, thus indicating that only molecular oxygen is required to complete the catalytic cycle.

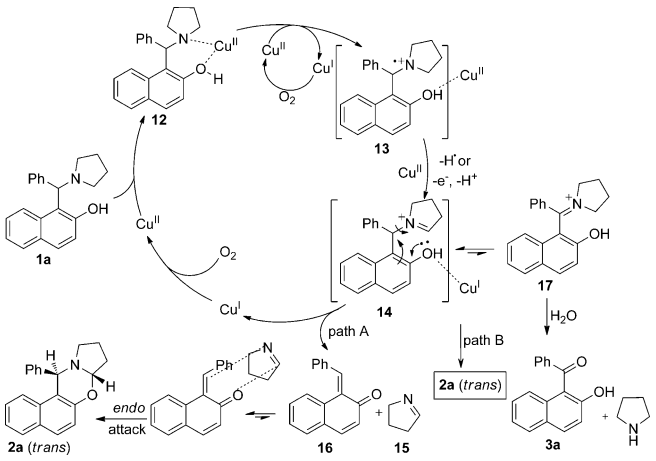


Scheme 3. Cross reaction between two substrates furnishing four products.



Scheme 4. Reaction using chiral substrate.

Based on the above findings, a tentative dual-pathway mechanism for the reaction may be proposed (Scheme 5). Compound **1a** may form iminium salt **14** through a single-electron transfer (SET) to Cu^{II}, which would form the intermediate ammoniumyl radical cation **13**, followed by subsequent loss of an H radical (or a combination of electron and H^+).[8d] Release of the cyclic imine **15**, with simultaneous formation of *o*-quinone methide **16**, would be followed by *endo*-[4+2] cycloaddition between the two to afford 2,3-dihydro-1,3-oxazine **2a** (path A). The *o*-quinone methide **16** has been trapped and characterized (Scheme S5). Partial retention of enantiomeric purity of the product **2a′** (Scheme 4) indicates the possibility of intramolecular cycli-



Scheme 5. Proposed mechanism.

zation of iminium salt **14** to afford product **2a** through C–O bond formation without disturbing the chiral center (path B). Cu^{I} would presumably be reoxidized to Cu^{II} by atmospheric oxygen. The reaction of ketone **3a** with pyrrolidine to form **17**, and eventually to produce **2a** by iminium rearrangment, was not observed under the reaction conditions (Scheme 5).[21]

To gain more insight into the SET mechanism, the model reaction was performed in the presence of radical scavengers such as 2,6-di-*tert*-butyl-4-methyl phenol (BHT) and thiophenol (1 equiv of each). A significant drop in yield was observed and only a trace of product **2a** was isolated, thus suggesting that this reaction includes a radical process. A full understanding of the mechanism will require further investigation.

The *trans* diastereoselectivity in the naphtho analogues can be explained by considering the more stable pseudo (*Z*)-*o*-naphthoquinone methide[22] as the reacting species (Figure 1a) and the less sterically hindered *endo* transition state

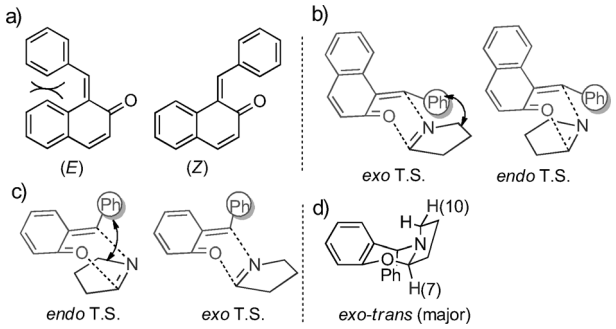


Figure 1. a) Steric repulsion destabilizes the *E* form. b) Steric repulsion in the *exo* transition state. c) Steric repulsion in the *endo* transition state. d) W coupling. T.S. = transition state.

(Figure 1b) for the cycloaddition reaction (Scheme 5, path A). Alternatively, the iminium ion **14** could be cyclized directly by attack of OH group on the iminium carbon, giving only the *trans* product because of the naphthyl ring, which prevents the free rotation of the phenyl substituent through the stereogenic center. The X-ray structure of compound **2j** confirms the expected *trans* stereochemistry (Figure S2).

For the phenolic compounds (**2t**–**x**) the more stable (*E*)-*o*-quinone methide[23] produced the *trans* diastereomer as the major product through the more favorable *exo*-selective transition state (Figure 1c). The *cis*/*trans* ratio was also supported by ^{1}HNMR and COSY spectrum, where W coupling ($^{4}J = 1.68$ Hz for **2u**) between the protons on C7 and C10 indicate that the *trans* diastereomer was the major product (Figure 1d).

Amine derivatives containing an aliphatic hydroxy group delivered the corresponding 1,3-oxazines (**2aa** and **2bb**) in lower yields, but as the diastereomerically pure *trans* isomer in both cases (Scheme 2).[17n] Here, an *o*-quinone methide cannot form and only intramolecular cyclization could be taking place, where the final stereochemistry would be controlled by the existing asymmetric center.

In conclusion, we have developed a copper-mediated intramolecular α-functionalization of tertiary amines through C–H bond oxidative activation (benzylic and non-benzylic) to synthesize diverse dihydro-1,3-oxazines through C–O bond formation. The method is very simple and uses inexpensive $Cu(OAc)_2{\cdot}H_2O$ as the catalyst. This conversion can be efficiently performed in an open vessel without the addition of external co-oxidants or additives. Neither dry solvent nor precautions for an inert atmosphere are required. Most importantly, naphthoxazines can be produced with 100% diastereoselectivity. The present convenient method for the synthesis of benzo- or naphtho-2,3-dihydro-1,3-oxazines should be of great utility in medicinal chemistry. Further mechanistic studies and applications of the reaction and the biological activities of the above compounds and analogues will be disclosed in due course.

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[1] a) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; b) M. Klussmann, D. Sureshkumar, *Synthesis* **2011**, 353; c) W.-J. Yoo, C.-J. Li, *Top. Curr. Chem.* **2010**, *292*, 281; d) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301; e) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; f) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928; g) Z. Shi, F. Glorius, *Angew. Chem.* **2012**, *124*, 9354; *Angew. Chem. Int. Ed.* **2012**, *51*, 9220; h) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464.

[2] a) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069; b) S.-I. Murahashi, Y. Imada in *Transition Metals for Organic Synthesis*, *Vol. 2*, *2nd ed.* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 497; c) X. Z. Shu, X. F. Xia, Y. F. Yang, K. G. Ji, X. Y. Liu, Y. M. Liang, *J. Org. Chem.* **2009**, *74*, 7464; d) G. Jiang, J. Chen, J. S. Huang, C. M. Che, *Org. Lett.* **2009**, *11*, 4568; e) K. M. Jones, M. Klussmann, *Synlett* **2012**, *23*, 159; f) K. Alagiri, K. R. Prabhu, *Org. Biomol. Chem.* **2012**, *10*, 835.

[3] a) S.-I. Murahashi, D. Zhang, *Chem. Soc. Rev.* **2008**, *37*, 1490; b) A. G. Condie, J. C. Gonz'alez-Go'mez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464; c) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny, D. C. Fabry, *Chem. Commun.* **2011**, *47*, 2360; d) D. B. Freeman, L. Furst, A. G. Condie, C. R. J. Stephenson, *Org. Lett.* **2012**, *14*, 94.

[4] a) W. Han, A. R. Ofial, *Chem. Commun.* **2009**, 5024; b) W. Han, P. Mayer, A. R. Ofial, *Adv. Synth. Catal.* **2010**, *352*, 1667; c) M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnurch, *Chem. Commun.* **2010**, *46*, 8836; d) H. Richter, O. G. Mancheno, *Eur. J. Org. Chem.* **2010**, 4460; e) P. Liu, C.-Y. Zhou, S. Xiang, C.-M. Che, *Chem. Commun.* **2010**, *46*, 2739; f) C. M. R. Volla, P. Vogel, *Org. Lett.* **2009**, *11*, 1701.

[5] A. J. Catino, J. M. Nichols, B. J. Nettles, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 5648.

[6] a) S. Singhal, S. L. Jain, B. Sain, *Chem. Commun.* **2009**, 2371; b) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, 3169.

[7] a) L. Huang, X. Zhang, Y. Zhang, *Org. Lett.* **2009**, *11*, 3730; b) L. Chu, X. Zhang, F.-L. Qing, *Org. Lett.* **2009**, *11*, 2197; c) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672; d) Z. Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590; e) O. Basle, N. Borduas, P. Dubois, J. M. Chapuzet, T.-H. Chan, J. Lessard, C.-J.

Li, *Chem. Eur. J.* **2010**, *16*, 8162; f) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968; g) M. Niu, Z. Yin, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 3961; h) O. Baslé, C.-J. Li, *Org. Lett.* **2008**, *10*, 3661; i) G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 10613; *Angew. Chem. Int. Ed.* **2011**, *50*, 10429.

[8] a) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Fare's, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106; b) O. Baslé, C.-J. Li, *Chem. Commun.* **2009**, 4124; c) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317; d) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068; e) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem.* **2011**, *123*, 11256; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062.

[9] a) L. Huang, T. Niu, J. Wu, Y. Zhang, *J. Org. Chem.* **2011**, *76*, 1759; b) M. Nishino, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 6447; c) F. Yang, J. Li, J. Xie, Z.-Z. Huang, *Org. Lett.* **2010**, *12*, 5214; d) X. Ye, C. Xie, Y. Pan, L. Han, T. Xie, *Org. Lett.* **2010**, *12*, 4240; e) O. Baslé, C.-J. Li, *Green Chem.* **2007**, *9*, 1047; f) J. Chen, B. Liu, D. Liu, S. Liu, J. Cheng, *Adv. Synth. Catal.* **2012**, *354*, 2438; g) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810; h) Y. Shen, Z. Tan, D. Chen, X. Feng, M. Li, C.-C. Guo, C. Zhu, *Tetrahedron* **2009**, *65*, 158.

[10] a) P. G. Gomez, H. P. Pabon, M. A. Carvajal, J. M. Rincon, *Rev. Colomb. Cienc. Quim.-Farm.* **1985**, *8*, 15; b) K. Waisser, K. Gregor, L. Kubicova, V. Klimesova, J. Kunes, M. Machacek, J. Kaustova, *Eur. J. Med. Chem.* **2000**, *35*, 733.

[11] a) Z. Bouaziz, J. Riondel, A. Mey, M. Berlion, J. Villard, H. Filliond, *Eur. J. Med. Chem.* **1991**, *26*, 469; b) B. A. Arthington-Skaggs, M. Motley, D. W. Warnock, C. J. Morrison, *J. Clin. Microbiol.* **2000**, *38*, 2254.

[12] a) J. B. Chylinska, T. Urbanski, M. Mordarski, *J. Med. Chem.* **1963**, *6*, 484; b) L. Benameur, Z. Bouaziz, P. Nebois, M. H. Bartoli, M. Boitard, H. Fillion, *Chem. Pharm. Bull.* **1996**, *44*, 605.

[13] a) B. P. Mathew, A. Kumar, S. Sharma, P. K. Shula, M. Nath, *Eur. J. Med. Chem.* **2010**, *45*, 1502; b) E. Petrlíková, K. Waisser, H. DiviŠova, P. Husaková, P. Vrabcova, J. Kuneš, K. Kolár, J. Stolariková, *Bioorg. Med. Chem.* **2010**, *18*, 8178.

[14] a) O. S. Pedersen, E. B. Pedersen, *Synthesis* **2000**, 479; b) A. J. Cocuzza, D. R. Chidester, B. C. Cordova, S. Jeffrey, R. L. Parsons, L. T. Bacheler, S. E. Viitanen, G. L. Trainor, S. S. Ko, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1177.

[15] a) J. N. Joyce, S. Presgraves, L. Renish, S. Borwege, D. H. Osredkar, M. Replogle, M. PazSoldan, M. J. Millan, *Exp. Neurol.* **2003**, *184*, 393; b) P. Zhang, E. A. Terefenko, A. Fensome, Z. Zhang, Y. Zhu, J. Cohen, R. Winneker, J. Wrobel, J. Yardley, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 787.

[16] a) C. Cimarelli, G. Palmieri, E. Volpini, *Tetrahedron* **2001**, *57*, 6089; b) Y. Dong, J. Sun, X. Wang, X. Xu, L. Cao, Y. Hu, *Tetrahedron: Asymmetry* **2004**, *15*, 1667; c) X. Wang, Y. Dong, J. Sun, X. Xu, R. Li, Y. Hu, *J. Org. Chem.* **2005**, *70*, 1897; d) N. Yamazaki, T. Ito, C. Kibayashi, *Org. Lett.* **2000**, *2*, 465; e) G. Cheng, X. Wang, D. Su, H. Liu, F. Liu, Y. Hu, *J. Org. Chem.* **2010**, *75*, 1911; f) J. D. Butler, D. M. Solano, L. I. Robins, M. J. Haddadin, M. J. Kurth, *J. Org. Chem.* **2008**, *73*, 234; g) I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos, N. Maulide, *Angew. Chem.* **2012**, *124*, 1986; *Angew. Chem. Int. Ed.* **2012**, *51*, 1950; h) J. Lu, X. Xu, S. Wang, C. Wang, Y. Hu, H. Hu, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2900.

[17] a) W. J. Burke, *J. Am. Chem. Soc.* **1949**, *71*, 609; b) W. J. Burke, M. J. Kolbezen, C. W. Stephens, *J. Am. Chem. Soc.* **1952**, *74*, 3601; c) W. J. Burke, K. C. Murdock, G. Ec, *J. Am. Chem. Soc.* **1954**, *76*, 1677; d) W. J. Burke, R. J. Reynolds, *J. Am. Chem. Soc.* **1954**, *76*, 1291; e) W. J. Burke, C. R. Hammer, C. Weatherbee, *J. Org. Chem.* **1961**, *26*, 4403; f) D. L. Fields, J. B. Miller, D. D. Reynolds, *J. Org. Chem.* **1962**, *27*, 2749; g) A. R. Katritzky, Y.-J. Xu, R. Jain, *J. Org. Chem.* **2002**, *67*, 8234; h) W. J. Burke, C. W. Stephens, *J. Am. Chem. Soc.* **1952**, *74*, 1518; i) B. P. Mathew, M. Nath, *J. Heterocycl. Chem.* **2009**, *46*, 1003; j) Z. Tang, Z. Zhu, Z. Xia, H. Liu, J. Chen, W. Xia, X. Ou, *Molecules* **2012**, *17*, 8174; k) C.-K. Chen, A. G. Hortmann, M. R. Marzabadi, *J. Am. Chem. Soc.* **1988**, *110*, 4829; l) F. Kienzle, *Tetrahedron Lett.* **1983**, *24*, 2213; m) M. Okimoto, K. Ohashi, H. Yamamori, S. Nishikawa, M. Hoshi, T. Yoshida, *Synthesis* **2012**, *44*, 1315; n) C. L. Mathis, B. M. Gist, C. K. Frederickson, K. M. Midkiff, C. C. Marvin, *Tetrahedron Lett.* **2013**, *54*, 2101; o) J. Xuan, Z.-J. Feng, S.-W. Duan, W.-J. Xiao, *RSC Adv.* **2012**, *2*, 4065; p) G. Pandey, G. Kumaraswamy, P. Y. Reddy, *Tetrahedron* **1992**, *48*, 8295.

[18] a) N. Cohen, J. F. Blout, R. J. Lopresti, D. P. Trullinger, *J. Org. Chem.* **1979**, *44*, 4005; b) E. M. Campl, W. R. Jackson, Q. J. McCubbin, A. E. Trnacek, *J. Chem. Soc. Chem. Commun.* **1994**, *24*, 2763; c) M. Campi, W. R. Jackson, Q. J. McCubbin, A. E. Trnacek, *Aust. J. Chem.* **1996**, *49*, 219; d) I. Azatmári, F. Fülöp, *Tetrahedron Lett.* **2011**, *52*, 4440.

[19] M. Periasamy, S. Anwar, M. N. Reddy, *Indian J. Chem. Sect. B* **2009**, *48*, 1261.

[20] **1a′**: $[\alpha]_D^{20} = +176.2°$ ($c = 1.3$, $CHCl_3$), $ee = 91\%$, chiralpak AD-H column, 95:5 hexanes/isopropanol, flow rate $= 0.5\ mL\,min^{-1}$, $R_t = 11.38$ (major), 13.57 (minor); **2a′:** $[\alpha]_D^{20} = +39.0°$ ($c = 1.2$, $CHCl_3$), $ee = 19\%$, chiralpak AD-H column, hexanes, flow rate $= 0.3\ mL\,min^{-1}$, $R_t = 19.85$ (minor), 25.53 (major).

[21] L. Ma, W. Chen, D. Seidel, *J. Am. Chem. Soc.* **2012**, *134*, 15305.

[22] A. R. Katritzky, X. Lan, *Synthesis* **1992**, 761.

[23] a) R. W. Van De Water, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367; b) A. Arduini, A. Bosi, A. Pochini, R. Ungaro, *Tetrahedron* **1985**, *41*, 3095.

