COMMUNICATIONS

DOI: 10.1002/adsc.201200731

Mild Metal-Free Intramolecular Oxidative Alkylation of a C_{sp3}–H Bond Adjacent to a Nitrogen Atom: A Versatile Approach to Ring-Fused Tetrahydroquinolines

Gen Zhang,[a] Shoulei Wang,[a] Yunxia Ma,[a] Weidong Kong,[a] and Rui Wang[a,b,*]

[a] Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Life Sciences, State Key Laboratory of Applied Organic Chemistry and Institute of Biochemistry and Molecular Biology, Lanzhou University, Lanzhou 730000, People's Republic of China
E-mail: wangrui@lzu.edu.cn
[b] State Key Laboratory of Chiroscience, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, People's Republic of China

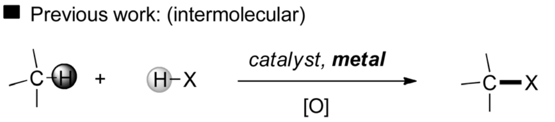
Received: August 15, 2012; Published online: February 27, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200731.

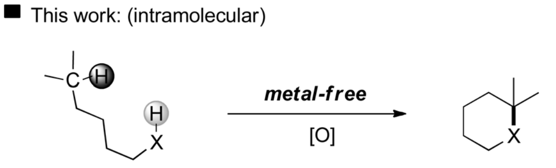
Abstract: A metal-free intramolecular oxidative cross-coupling reaction for the constructing C_{sp3}–C_{sp3} bonds mediated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under mild conditions was realized for the first time. This novel strategy provides a simple, efficient, and environmentally friendly access to diverse ring-fused tetrahydroquinoline derivatives.

Keywords: intramolecular reaction; metal-free conditions; oxidative cross-coupling; tetrahydroquinolines

The oxidative coupling reaction has been developed to become one of the most efficient and atom-economical strategies for forging new bonds through direct coupling of two C–H or heteroatom–H bonds.[1] The prospect of concise synthesis of complex molecules from simple starting materials under mild conditions makes this reaction particularly attractive. Amongst such reactions, the oxidative coupling of amines with various nucleophiles catalyzed by transition metals has received considerable attention,[2] and tremendous progress has been made in this fascinating field since the pioneering works of Murahashi and Li.[3] Despite the remarkable achievements documented, the majority of them focused on intermolecular reactions [Eq. (1)], with a few examples reported on the intramolecular reactions.[4] On the other hand, these reactions usually require the use of a transition metal, such as Cu, Fe, Pd, Pt, V, Au and Ru. However, transition metal-catalyzed oxidative coupling suffers from some drawbacks in industrial applications such as its high cost, air- and moisture-sensitivity, and the possibility of toxic trace metal contaminants. For these reasons, C–C or C–hetero atom bonds should be formed with the same levels of efficiency and selectivity as in transition metal-catalyzed reactions but without the addition of any transition metal, which is called the metal-free cross-coupling and indeed has attracted increasing attention in recent years.[5] Herein, we describe our first contribution on the intramolecular metal-free oxidative coupling of amines under mild conditions [Eq. (2)].



(1)

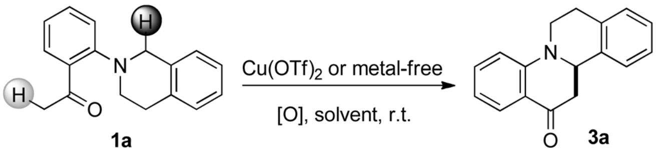


(2)

Ring-fused tetrahydroquinoline derivatives are widely used in organic synthesis and pharmaceutical chemistry owing to their significant applications as building blocks and for their intriguing biological activities.[6] Traditional methodologies for the formation of these privileged heterocycles mainly include the Povarov reaction,[7] reduction of quinolines[8] and a 1,5-hydride transfer/cyclization process.[9] However, the intramolecular oxidative C_{sp3}–H alkylation of amines, an alternative straightforward approach that could afford tetrahydroquinolines, has not been developed for their synthesis. As part of our continuous in-

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

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



Entry	Solvent	Cu(OTf)$_2$ [mol%]	Oxidant [1.1 equiv.]	Yield [%][b]
1	DCM	10	DDQ	66
2	DCM	-	DDQ	67
3	DCM	-	PhI(OAc)$_2$	61
4	DCM	-	*t*-BuOOH	56
5	DCM	-	BQ	57
6	DCM	-	*t*-BuOOtBu	35
7	DCM	-	BzOOBz	41
8	DCM	-	IBX	36
9	DCM	-	H_2O_2	37
10	DCM	-	O_2 (1 atm)	<10
11	DCM	-	Cu(OAc)$_2$	38
12	DCM	-	AgOAc	<10
13	DCM	-	Ag_2CO_3	23
14	DCM	-	MnO_2	39
15	DCM	-	$Na_2S_2O_8$	26
16	**THF**	-	**DDQ**	**74**
17	toluene	-	DDQ	64

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.2 mmol) in the presence of oxidant (0.22 mmol) in DCM (1.0 mL) at room temperature for 12 h.

[b] Isolated yield

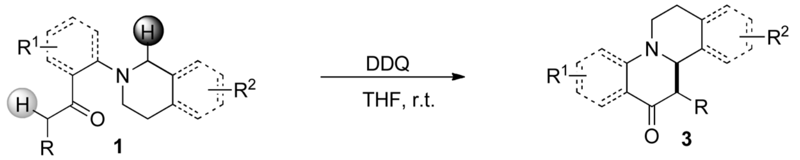
terest in the functionalization of amines,[10] we recently reported the first example of copper-catalyzed oxidative cross-coupling reactions of amines with activated methylenes and olefins for C_{sp3}–H alkylation and C_{sp3}–H olefination of tertiary amines for the synthesis of C-1 alkyled and C-1 alkenylated tetrahydroisoquinolines.[10a,b] Encouraged by these successful efforts and aiming to develop other unprecedented transformations, herein we describe our recent contribution on intramolecular oxidative couplings of tertiary amines for the synthesis of ring-fused tetrahydroquinoline derivatives.

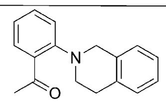
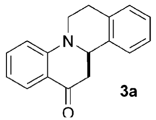
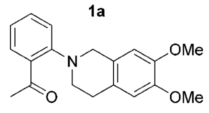
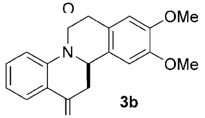
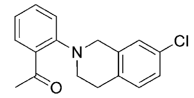
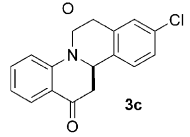
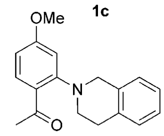
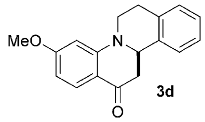
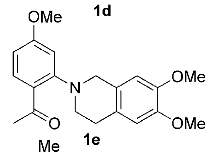
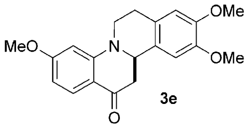
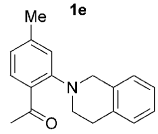
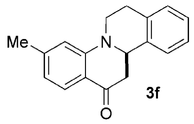
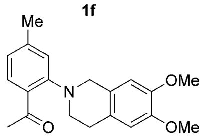
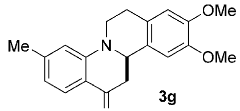
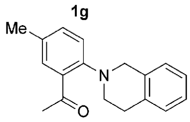
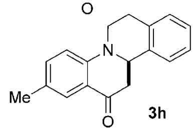
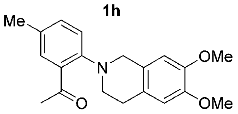
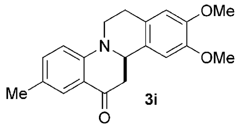
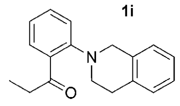
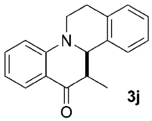
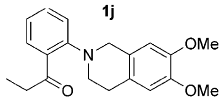
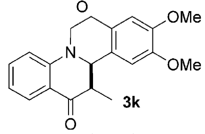
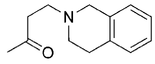
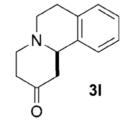
As 2,3-dichloro-5,6-dicyanoquinone (DDQ) has been widely used as an efficient oxidant in several recent oxidative coupling reactions,[11] we started our study on the DDQ-mediated intramolecular oxidative coupling reaction of 1-{2-[3,4-dihydroisoquinolin-2(1*H*)-yl]phenyl}ethanone (**1a**) in the present of Cu(OTf)$_2$ in DCM at room temperature. The reaction gave a moderate yield (66%) when using a 1.1 equiv. amount of DDQ (Table 1, entry 1), while using DDQ alone gave the same yield (entry 2, 67%). Other oxidants including organic oxidants (Table 1, entries 3–10) and metal oxidants (Table 1, entries 11–15) were also used to improve the activity of this reaction. However, neither the organic oxidants nor the metal oxidants could give the desired product in good yield. Solvent optimization results showed that THF was a better solvent with regard to the yield (Table 1, entries 16 and 17).

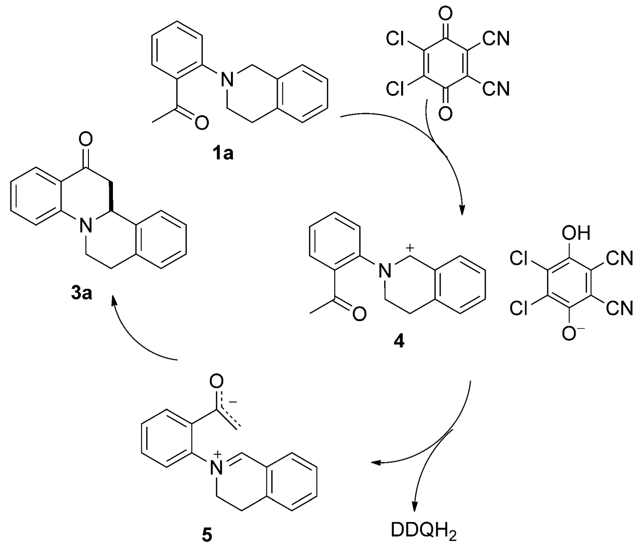
With the best reaction conditions established, the scope of substrates for the metal-free intramolecular oxidative coupling reactions for the synthesis of varous ring-fused tetrahydroquinoline derivatives was then studied. In general, the reaction proceeded well to afford the desired products in good to excllent yields. The protocol was found to be tolerant to both electron-withdrawing and electron-donating substituents in R^1 and R^2. When R^1 was an electron-donating substituent, a worse result was obtained (Table 2, entries 1 and 4, the yield declined from 73% to 48%), while R^2 as a electron-donating group could greatly improve the yield (compare entries 4 and 5, the yield improved from 48% to 95%). This might be due to the fact that the electron-donating substituent in R^1 reduces the activity of ketone, but the electron-donating group on R^2 enhances the activity of the tetrahydroisoquinoline to form an iminium cation. The same result could be seen from entries 1 and 2, while an electron-withdrawing group slightly hindered the reaction (entry 3, yield reduced from 73% to 62%), although a good yield could be obtained when the reaction was carried out at 50 °C. This might be due to the fact that the electron-donating substituent in R^2 enhances the reactivity of tetrahydroisoquinoline, while an electron-withdrawing group plays an opposite role. The electrically neutral methyl substituent on the *meta* position gave a better yield of desired product than a methyl substituent on the *para* position (Table 2, entries 6 and 8), although this could be avoided by introducing a methoxy group to the aromatic ring of tetrahydroisoquinoline (Table 2, entries 7 and 9). When R was methyl, a better yield was achieved than with H, and excellent diastereoselectivitycould be achieved (Table 2, entries 10 and 11, *dr* up to 20/1). Finally, 4-[3,4-dihydroisoquinolin-2(1*H*)-yl]butan-2-one could react under this system to yield the desirable product in 58% yield when the reaction was carried at 50 °C (Table 2, entry 12).

The possible pathways of this novel intramolecular oxidative coupling reaction is assumed to involve a single-electron transfer (SET) radical mechanism.[12] Under DDQ, a hydrogen atom could be abstracted from the C-1 position of **1a** to afford the radical cation **4**, which was subsequently transferred to iminium cation **5** as a key intermediate (Scheme 1). To check the intermediacy of a radical cation, TEMPO (2,2,6,6-tetramethyl-piperidin-1-oxyl), a radical inhibitor, was added to this reaction system; there was no significant change in the yield of the intramolecular coupling product and the addition product of **1a** with TEMPO was not formed. These results indicate that a radical cation might be involved but that the irreversible hydrogen transfer could be so rapid that TEMPO cannot capture this radical cation, however,

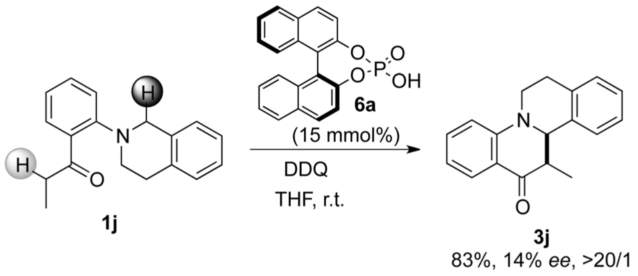
Table 2. Investigating the scope of the procedure.[a]



Entry	Subsrate 1	Time [h]	Product 3	Yield [%][b] [dr [%][c]]
1	 1a	12	 3a	73
2	 1b	10	 3b	85
3	 1c	14	 3c	62 (86)[d]
4	 1d	12	 3d	48
5	 1e	10	 3e	95
6	 1f	12	 3f	75
7	 1g	12	 3g	90
8	 1h	10	 3h	89
9	 1i	10	 3i	91
10	 1j	12	 3j	81 (>20/1)[c]
11	 1k	12	 3k	74 (>20/1)[c]
12	 1l	16	 3l	58 [d]



Scheme 1. Proposed mechanism for metal-free intramolecular oxidative coupling.



Scheme 2. Asymmetric induction in the metal-free intramolecular oxidative coupling.

a little amount of this radical cation can be captured by 2,6-di-*tert*-butyl-4-methylphenol (BHT; about 30%, the yield of **3a** decreased from 73 to 41%). After formation of the iminium intermediate **5**, the intramolecula electrophilic addition to enol occurs to give the final product **3a**.

For the development of an asymmetric intramolecular oxidative coupling reaction mediated by DDQ under mild conditions for the synthesis of chiral ring-fused tetrahydroquinolines, we examined various chiral organocatalysts (for the detail, see the Supporting Information). The coupling product **3j** was obtained with 14% *ee* when the chiral phosphoric acid **6a** was used (Scheme 2).

In summary, we have described a novel metal-free intramolecular oxidative cross-coupling reaction for constructing C_{sp3}–C_{sp3} bonds mediated by DDQ under mild conditions with good to excellent yields (48–95%). This method provides an alternative approach to current transition metal-catalyzed oxidative cross-coupling, and provides an efficient and environmentally friendly way to access diverse ring-fused tetrahydroquinoline derivatives in one step from basic starting materials and under a direct, efficient, mild and atom-economical process. The development of this novel metal-free system in other oxidative coupling reactions is being pursued.

Experimental Section

For detailed experimental procedures, spectral data and characterization see the Supporting Information.

Typical Experimental Procedure for the Preparation of Ring-Fused Tetrahydroquinolines

A solution 2,3-dichloro-5,6-dicyanoquinone (DDQ, 0.22 mmol) in anhydrous THF (0.6 mL) was slowly added dropwise to the solution of *N*-aryltetrahydroisoquinolin **1** (0.2 mmol) in anhydrous THF (0.4 mL) at room temperature for 0.5 h, and then the resultant reaction mixture was stirred at room temperature for the appropriate time. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate/hexane 1:10). After filtration the solvent was removed at reduced pressure to give the pure products.

Acknowledgements

We are grateful for the grants from the National Natural Science Foundation of China (nos. 20932003, 91213302, and 21272101) and the Key National S&T Program “Major New Drug Development” of the Ministry of Science and Technology of China (2012ZX09504-001-003).

References

[1] Recent reviews on oxidative coupling reactions: a) J.-E. Bäckvall, *Modern Oxidation Methods*, 2nd edn., Wiley-VCH, Weinheim, **2011**; b) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761–2776; c) S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. B. Ripin, *Chem. Rev.* **2006**, *106*, 2943–2989; d) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424; e) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew.*

---

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.2 mmol) in the presence of DDQ (0.22 mmol) in THF (1.0 mL) at room temperature for 10–16 h.

[b] Isolated yield.

[c] The diastereomeric ratio, determined by ^{1}H NMR spectroscopy.

[d] The reaction was carried out at 50 °C

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Chem. **2011**, *123*, 11256–11283; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062–11087.

[2] Selected reviews on oxidative coupling of amines: a) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084; b) S.-I. Murahashi, D. Zhang, *Chem. Soc. Rev.* **2008**, *37*, 1490–1501; c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; d) C. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; e) K. M. Jones, M. Klussmann, *Synlett* **2012**, 159–162.

[3] a) N. Sasamoto, C. Dubs, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2006**, *128*, 14010–14011; b) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183–7186; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075–7078; c) A. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem.* **2010**, *122*, 5124–5128; *Angew. Chem. Int. Ed.* **2010**, *49*, 5004–5007; d) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673; e) S.-I. Murahashi, T. Nakae, H. Terai, N. Komiya, *J. Am. Chem. Soc.* **2008**, *130*, 11005–11012; f) J. M. Allen, T. H. Lambert, *J. Am. Chem. Soc.* **2011**, *133*, 1260–1262; g) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811; h) A. J. Catino, J. M. Nichols, B. J. Nettles, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649; i) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933; j) K. M. Jones, P. Karier, M. Klussmann, *ChemCatChem* **2012**, *4*, 51–54; k) O. Baslé, C.-J. Li, *Chem. Commun.* **2009**, *27*, 4124–4126; l) O. Baslé, C.-J. Li, *Org. Lett.* **2008**, *10*, 3661–3663; m) O. Baslé, N. Borduas, P. Dubois, J.-M. Chapuzet, T.-K. Lessard, J. Chan, C.-J. Li, *Chem. Eur. J.* **2010**, *16*, 8162–8166; n) O. Baslé, C.-J. Li, *Green Chem.* **2007**, *9*, 1047–1050; o) J. Xie, H. Li, J. Zhou, Y. Cheng, C. Zhu, *Angew. Chem.* **2012**, *124*, 1278–1281; *Angew. Chem. Int. Ed.* **2012**, *51*, 1252–1255.

[4] a) G. Pandey, G. Kumaraswamy, *Tetrahedron Lett.* **1988**, *29*, 4153–4156; b) C. K. Chen, A. G. Hortmann, M. R. Marzabadi, *J. Am. Chem. Soc.* **1988**, *110*, 4829–4831; c) Y. W. Son, T. H. Kwon, J. K. Lee, A. N. Pae, J. Y. Lee, Y. S. Cho, S.-J. Min, *Org. Lett.* **2011**, *13*, 6500–6503.

[5] a) S. Yanagisawa, K. Ueda, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 4673–4676; b) G. Deng, K. Ueda, S. Yanagisawa, K. Itami, C. Li, *Chem. Eur. J.* **2009**, *15*, 333–337; c) Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto, T. Dohi, *J. Am. Chem. Soc.* **2009**, *131*, 1668–1669; d) A. S.-K. Tsang, M. H. Todd, *Tetrahedron Lett.* **2009**, *50*, 1199–1202; e) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 16737–16740; f) E. Shirakawa, K. Itoh, T. Higashino, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539; g) Y. Yuan, I. Thome, S. H. Kim, D. Chen, A. Beyer, J. Bonnamour, E. Zuidema, S. Chang, C. Bolm, *Adv. Synth. Catal.* **2010**, *352*, 2892–2898; h) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li, Z.-J. Shi, *Nat. Chem.* **2010**, *2*, 1044–1049; i) E. Shirakawa, X. Zhang, T. Hayashi, *Angew. Chem.* **2011**, *123*, 4767–4770; *Angew. Chem. Int. Ed.* **2011**, *50*, 4671–4674; j) T. He, L. Yu, L. Zhang, L. Wang, M. Wang, *Org. Lett.* **2011**, *13*, 5016–5019; k) M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.* **2011**, *13*, 98–101; l) S. Murarka, A. Studer, *Adv. Synth. Catal.* **2011**, *353*, 2708–2714; m) Y. Qiu, Y. Liu, K. Yang, W. Hong, Z. Li, Z. Wang, Z. Yao, S. Jiang, *Org. Lett.* **2011**, *13*, 3556–3559; n) K. Ito, H. Tamashima, N. Iwasawa, H. Kusama, *J. Am. Chem. Soc.* **2011**, *133*, 3716–3719.

[6] a) D. H. Barton, K. Nakanishi, O. Meth-Cohn, *Comprehensive Natural Chemistry*; Elsevier, Oxford, **1999**, Vols. 1–9; b) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031–15038.

[7] a) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070–13071; b) V. A. Glushkov, A. G. Tolstikov, *Russ. Chem. Rev.* **2008**, *77*, 137–159; c) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721–2750; d) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. P. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599; e) G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi, A. Ricci, *Chem. Commun.* **2010**, *46*, 327–329.

[8] a) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765–3768; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683–3686; b) Y. G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366; c) N. Mrsic, L. Lefort, J. A. F. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2008**, *350*, 1081–1083; d) Q. S. Guo, D. M. Du, J. Xu, *Angew. Chem.* **2008**, *120*, 771–774; *Angew. Chem. Int. Ed.* **2008**, *47*, 759–762; e) X. B. Wang, Y. G. Zhou, *J. Org. Chem.* **2008**, *73*, 5640–5642; f) A. O'Byrne, P. Evans, *Tetrahedron* **2008**, *64*, 8067–8072.

[9] For racemic examples: a) W. Verboom, D. N. Reinhoudt, R. Visser, S. Harkema, *J. Org. Chem.* **1984**, *49*, 269–276; b) W. H. N. Nijhuis, W. Verboom, D. N. Reinhoudt, S. Harkema, *J. Am. Chem. Soc.* **1987**, *109*, 3136–3138; c) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180–12181; d) S. J. Pastine, D. Sames, *Org. Lett.* **2005**, *7*, 5429–5431; e) M. Tobisu, N. Chatani, *Angew. Chem.* **2006**, *118*, 1713–1715; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683–1684; f) C. Zhang, C. K. De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416–417; g) K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 402–403; h) D. Shikanai, H. Murase, T. Hata, H. Urabe, *J. Am. Chem. Soc.* **2009**, *131*, 3166–3167; i) S. Murarka, C. Zhang, M. D. Konieczynska, D. Seidel, *Org. Lett.* **2009**, *11*, 129–132; j) K. M. McQuaid, J. Z. Long, D. Sames, *Org. Lett.* **2009**, *11*, 2972–2975; k) C. Zhang, S. Murarka, D. Seidel, *J. Org. Chem.* **2009**, *74*, 419–422; l) K. Mori, T. Kawasaki, S. Sueoka, T. Akiyama, *Org. Lett.* **2010**, *12*, 1732–1735.

[10] a) G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 10613–10616; *Angew. Chem. Int. Ed.* **2011**, *50*, 10429–10432; b) G. Zhang, Y. Ma, S. Wang, Y. Zhang and R. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 12334–12337; c) G. Zhang, Y. Zhang, X. Jiang, W. Yan, and R. Wang, *Org. Lett.* **2011**, *13*, 3806–3809; d) G. Zhang, Y. Zhang, J. Yan, R. Chen, S. Wang, W. Yan, and R. Wang, *J. Org. Chem.* **2012**, *77*, 878–888.

[11] a) W. Tu, P. E. Floreancig, *Angew. Chem.* **2009**, *121*, 4637–4641; *Angew. Chem. Int. Ed.* **2009**, *48*, 4567–4571; b) L. Liu, P. E. Floreancig, *Angew. Chem.* **2010**, *122*, 6030–6033; *Angew. Chem. Int. Ed.* **2010**, *49*, 5894–5897; c) C. Guo, J. Song, S. W. Luo, L.-Z. Gong, *Angew. Chem.* **2010**, *122*, 5690–5694; *Angew. Chem. Int. Ed.* **2010**, *49*, 5558–5562; d) Y. Hayashi, T. Itoh, H. Ishikawa, *Angew. Chem.* **2011**, *123*, 4006–4010; *Angew. Chem. Int. Ed.* **2011**, *50*, 3920–3924; e) S.-L. Zhang, H.-

X. Xie, J. Zhu, H. Li, X.-S. Zhang, J. Li, W. Wang, *Nat. Commun.* **2011**, *2*, 211–217.

[12] a) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091–7093; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931–6933; b) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Farèes, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106–8109; c) H. H. Jung, P. E. Floreancig, *Tetrahedron* **2009**, *65*, 10830–10836.

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim