Transition Metals in Organic Synthesis, Part 111:[1] First Total Synthesis and Structural Revision of Antipathine A

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Received: 18.07.2013; Accepted: 01.08.2013

Abstract: We describe the first total synthesis of antipathine A and a revision of the original structural assignment.

Key words: alkaloids, catalysis, cyclisation, palladium

The structural diversity and the manifold biological activities of carbazole alkaloids have induced a strong interest in isolation and total synthesis of new members of this class of natural products.[1–5] Important natural sources are, for example, higher plants of the genera *Murraya*, *Clausena*, and *Glycosmis* of the family Rutaceae. Apart from classical procedures for construction of the carbazole framework, several new procedures using transition metals have been developed. We described an iron-mediated and a palladium-catalysed approach for the synthesis of carbazoles.[4,5]

In 2009, Qi et al. isolated antipathine A, a new carbazole alkaloid from the South China Sea black coral *Antipathes dichotoma*.[6] They postulated structure **1** for this natural product (Figure 1). Due to the inherent high strain of the 1,3-bridged ring system, Hill et al. questioned the structural assignment for antipathine A.[7] Based on the published spectroscopic data, we suggested structure **2** for antipathine A and developed a synthetic access to this compound using our methodology for carbazole construction (Scheme 1).

Compound **2** should be available by oxidative cyclisation of the diarylamine **3**. Two alternative routes have been considered for the synthesis of this diarylamine. Retrosynthetic analysis of **3** following route A suggests bromobenzene (**4**) and 6-amino-1,3-dimethylquinazoline-2,4-dione (**5**) as precursors, whereas route B leads to aniline (**6**) and 6-bromo-1,3-dimethylquinazoline-2,4-dione (**7**). The first approach (route A) starts from 2-amino-5-nitrobenzoic acid (**8**, Scheme 2). Condensation of **8** with urea afforded 6-nitroquinazoline-2,4-dione (**9**).[8] Double N-methylation of **9** using tetraethylammonium hydroxide and dimethyl sulfate led to 1,3-dimethyl-6-nitroquinazoline-2,4-dione (**10**),[9] which on catalytic hydrogenation provided 6-amino-1,3-dimethylquinazoline-2,4-dione (**5**). Buchwald–Hartwig amination of bromobenzene (**4**) with **5** using SPhos as ligand[10] afforded 1,3-dimethyl-6-phenylaminoquinazoline-2,4-dione (**3**). Using route A, the diarylamine **3** is available in four steps and 45% overall yield.

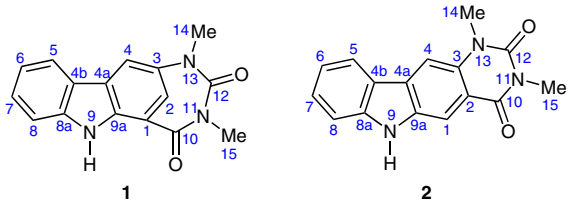
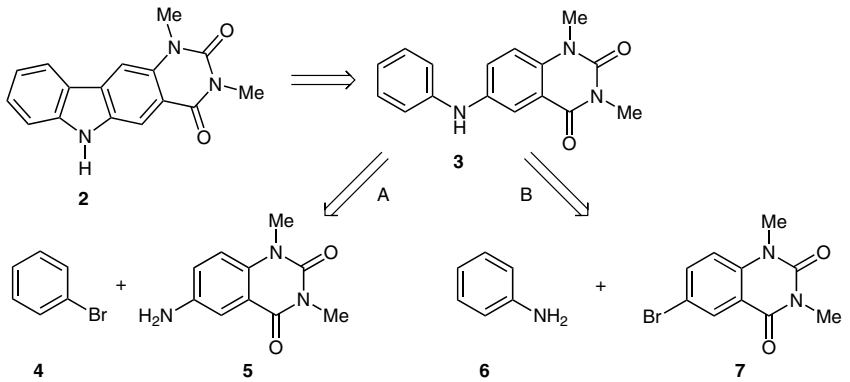


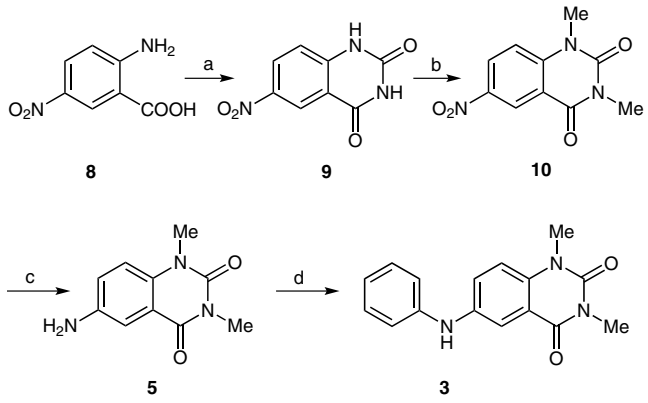
Figure 1 Originally reported (**1**)[6] and revised structure (**2**) of antipathine A

For the synthesis of diarylamine **3** via the alternative route B we used 2-amino-5-bromobenzoic acid (**11**) as starting material (Scheme 3). Condensation of compound **11** with urea led to 6-bromoquinazoline-2,4-dione (**12**). Subse-

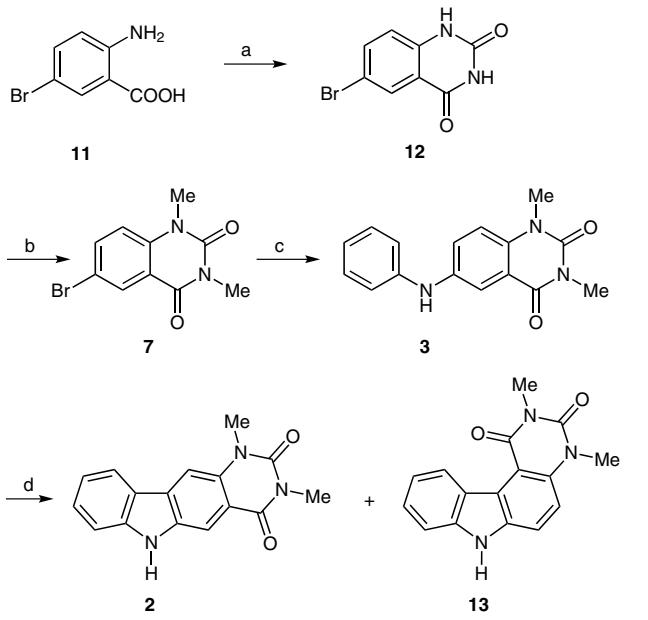


Scheme 1 Retrosynthetic analysis of antipathine A (**2**)

SYNLETT 2013, 24, 000A–000E
Advanced online publication: 21.08.2013
DOI: 10.1055/s-0033-1339655; Art ID: ST-2013-B0671-L



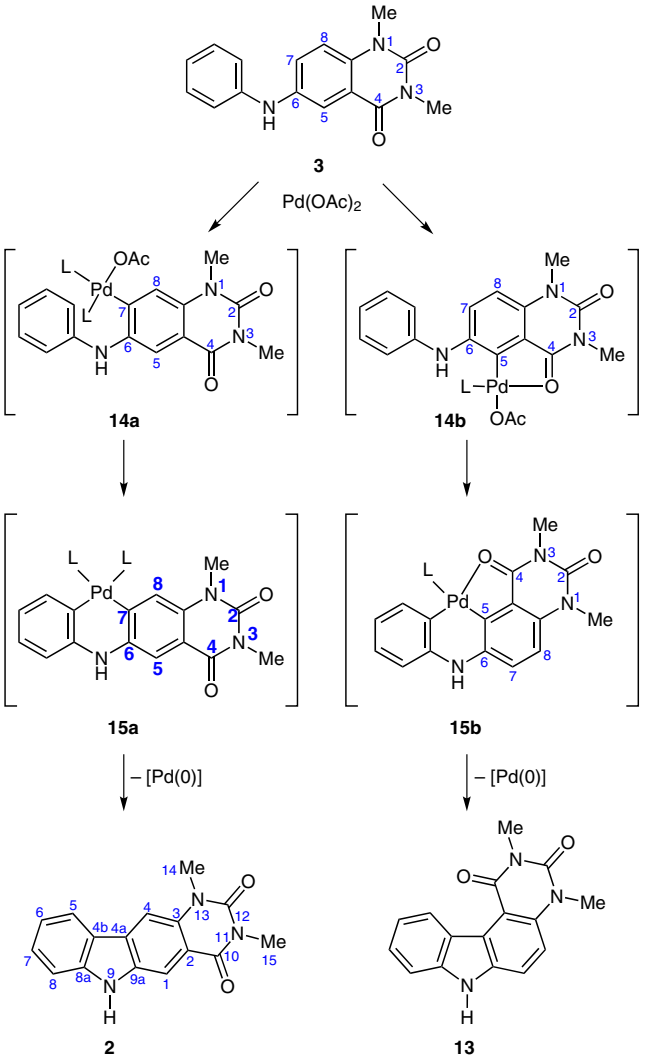
Scheme 2 Route A to the diarylamine **3**. *Reagents and conditions*: (a) urea (15 equiv), 150 °C, 25 h, 70%; (b) $Et_4N^+OH^-$ (2.5 equiv), Me_2SO_4 (4 equiv), H_2O, r.t., 1 h, 60 °C, 1 h, 77%; (c) 17 wt% Pd/C (10% Pd), H_2, CH_2Cl_2–EtOAc (1:1), r.t., 45 min, 93%; (d) PhBr (**4**, 1.1 equiv), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), Cs_2CO_3 (1.4 equiv), PhMe, 100 °C, 72 h, 89%.



Scheme 3 Route B to the diarylamine **3** and oxidative cyclisation. *Reagents and conditions*: (a) urea (20 equiv), 150 °C, 25 h, 94%; (b) $Et_4N^+OH^-$ (2.5 equiv), Me_2SO_4 (3 equiv), H_2O, r.t., 1 h, 60 °C, 1 h, 83%; (c) **7** (1.1 equiv), $PhNH_2$ (**6**, 1 equiv), $Pd(OAc)_2$ (7 mol%), SPhos (14 mol%), Cs_2CO_3 (1.4 equiv), PhMe, 100 °C, 71 h, 85%; (d) $Pd(OAc)_2$ (1.1 equiv), PivOH, 100 °C, 25 h, 23% **2**, 70% **13**.

quent twofold N-methylation to 6-bromo-1,3-dimethylquinazoline-2,4-dione (**7**) followed by Buchwald–Hartwig coupling with aniline (**6**) afforded the diarylamine **3**. Following route B, compound **3** was obtained in three steps and 66% overall yield.

The palladium(II)-mediated oxidative cyclisation of compound **3** in acetic acid solution led to the pyrimido[4,5-*c*]carbazole-1,3-dione **13** as major product in 68% yield (Scheme 3, Table 1).[11] The desired pyrimido[5,4-*b*]carbazole-2,4-dione **2**, presumably identical with antipathine A, was isolated in only 3% yield. However, using pivalic acid as solvent,[5j,5k,12] the regioisomeric carbazoles **2** and **13** were obtained in 93% yield and a ratio of 1:3. Thus, compound **2** could be isolated in 23% yield and fully characterised by its spectroscopic data.[13]



Scheme 4 Ortho-directed palladation by coordinative interaction of the C=O at C4 to palladium and non-directed palladation (L = AcOH, PivOH).

Table 1 Reaction Conditions for the Oxidative Cyclisation of **3**

Reaction conditions	Yield of **2** (%)	Yield of **13** (%)	Yield of **3** (%)[a]
$Pd(OAc)_2$ (1.1 equiv), AcOH, 100 °C, 2 h, Ar	3	68	8
$Pd(OAc)_2$ (1.1 equiv), PivOH, 100 °C, 25 h, Ar	23	70	7

[a] Re-isolated starting material.

Table 2 ^{1}H NMR Spectroscopic Data for Antipathine A[a]

Data (δ, ppm) reported for antipathine A[6]		Our data (δ, ppm) for antipathine A (**2**)	
3.57 (s)	15-H_3	3.57 (s)	15-H_3
3.66 (s)	14-H_3	3.66 (s)	14-H_3
7.35 (t, *J* = 7.5 Hz)	6-H	7.35 (t, *J* = 7.4 Hz)	6-H
7.60 (t, *J* = 7.5 Hz)	7-H	7.59 (t, *J* = 7.6 Hz),	7-H
7.66 (d, *J* = 7.5 Hz)	**5-H**	7.66 (d, *J* = 8.2 Hz)	**8-H**
8.14 (s)	4-H	8.14 (s)	4-H
8.42 (d, *J* = 7.5 Hz)	**8-H**	8.41 (d, *J* = 7.8 Hz)	**5-H**
8.66 (s)	**2-H**	8.65 (s)	**1-H**
12.73 (br s)	N–H	12.72 (br s)	N–H

[a] H atoms marked in bold have been wrongly assigned before.[6]

Table 3 ^{13}C NMR Spectroscopic Data for Antipathine A[a]

Data (δ, ppm) reported for antipathine A[6]		Our data (δ, ppm) for antipathine A (**2**)	
28.4	C15 (CH_3)	28.51	C15 (CH_3)
30.9	C14 (CH_3)	31.03	C14 (CH_3)
104.7	C4 (CH)	104.87	C4 (CH)
110.1	**C2** (CH)	110.19	**C1** (CH)
111.9	C8 (CH)	112.03	C8 (CH)
114.4	**C4a**	114.50	**C2**
119.5	C6 (CH)	119.62	C6 (CH)
122.0	C5 (CH)	122.18	C5 (CH)
122.8	C4b	122.91	C4b
128.4	C7 (CH)	128.46	C7 (CH)
129.7	**C1**	129.76	**C4a**
133.9	C3	133.94	C3
136.8	C9a	136.74	C9a
143.5	C8a	143.60	C8a
151.0	C12 (C=O)	151.09	C12 (C=O)
162.6	C10 (C=O)	162.71	C10 (C=O)

[a] C atoms marked in bold have been wrongly assigned before.[6]

The strong preference for compound **13** appears to be surprising, since the carbazole with the [*c*]-anellated pyrimidinedione ring represents the sterically more congested ring system. We assume that the C–H bond activation of **3** preferentially occurs in the position *ortho* to the carbonyl group via coordination of the oxygen to palladium.[14] This directed palladation leads to complex **14b** (Scheme 4). A second intramolecular C–H bond activation generates palladacycle **15b**. Reductive elimination of **15b** provides the pyrimido[4,5-*c*]carbazole-1,3-dione **13** which is observed as major product of these cyclisations. We have recently been able to isolate a palladacycle related to **15b** and demonstrated its reductive elimination to 4-substituted carbazoles.[14g] Nondirected palladation to complex **14a** followed by cyclopalladation to **15a** and reductive elimination ultimately affords the pyrimido[5,4-*b*]carbazole-2,4-dione **2**. Alternatively, palladacycle **15a** might also be formed by initial electrophilic palladation of the phenyl ring and subsequent cyclopalladation. Presumably, the increased steric demand of the pivalate ligand relative to an acetate ligand renders the nondirected palladation (metallation at the more easily accessible position C7 or at the phenyl ring) more competitive to the directed palladation (metallation at C5). Using pivalic acid as solvent leads to a cleaner course of the reaction,[5j,5k,12] and the pathway via complex **14a** and palladacycle **15a** leading to carbazole **2** is gaining importance relative to the route leading to isomer **13**.

Careful analysis of the NMR data for our synthetic compound **2** supported by COSY, NOESY, HMBC, and HSQC experiments led to a full assignment for all ^{1}H NMR and ^{13}C NMR signals (Table 2 and Table 3, Supporting Information).[13] Comparison of the spectroscopic data for our compound **2** with those published by Qi et al. for natural antipathine A revealed that several ^{1}H NMR and ^{13}C NMR signals have been wrongly assigned in the original publication which led to the incorrect structure.[6] In particular, the NMR signals for the following atoms had to be reassigned: 2-H as 1-H, 5-H as 8-H, 8-H as 5-H, C2 as C1, C4a as C2, and C1 as C4a (Table 2 and Table 3). Also some of the reported HMBC correlations were revised (Table 4). The combined spectroscopic data unambiguously confirm that carbazole **2** represents the correct structure for antipathine A.

In conclusion, we have developed a synthesis of carbazole **2** using a palladium-catalysed Buchwald–Hartwig coupling and a palladium-mediated oxidative cyclisation as key steps to construct the carbazole framework. Our approach provides carbazole **2** in four steps and 15% overall yield based on 2-amino-5-bromobenzoic acid (**11**). The spectroscopic data emphasise that the original structural assignment needs revision and confirm that the structure of our synthetic compound **2** is identical with natural antipathine A.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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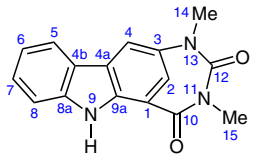
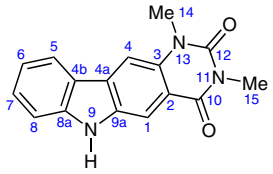
Table 4 Comparison of the Assignments for the HMBC Correlations Reported by Qi et al.[6] for **1** with our Corresponding Assignments for the Revised Structure of Antipathine A (**2**)[a]



1



2

HMBC correlations (δ, ppm) reported by Qi et al.[6]		HMBC correlations (δ, ppm) observed by us	
2-H/C1	8.66/129.7	**1-H/C4a**	8.65/129.76
2-H/C3	8.66/**104.7**	**1-H**/C3	8.65/**133.94**
2-H/C10	8.66/162.6	**1-H**/C10	8.65/162.71
4-H/C9a	8.14/136.8	4-H/C9a	8.14/136.74
4-H/C3	8.14/133.9	4-H/C3	8.14/133.94
4-H/**C4a**	8.14/114.4	4-H/**C2**	8.14/114.50
4-H/C4b	8.14/122.8	4-H/C4b	8.14/122.91
–	–	4-H/C1	8.14/110.19
–	–	4-H/C10	8.14/162.71
5-H/C4b	7.66/122.8	**8-H**/C4b	7.66/122.91
–	–	8-H/C6	7.66/119.62
6-H/C4b	7.35/122.8	6-H/C4b	7.35/122.91
6-H/C8	7.35/111.9	6-H/C8	7.35/112.03
–	–	6-H/C7	7.35/128.46
7-H/C8	7.60/111.9	–	–
7-H/C8a	7.60/143.5	7-H/C8a	7.59/143.60
–	–	7-H/C5	7.59/122.18
8-H/C8a	8.42/143.5	**5-H**/C8a	8.41/143.60
–	–	**5-H/C4a**	8.41/129.76
–	–	**5-H**/C7	8.41/128.46
14-H_3/C3	3.66/133.9	14-H_3/C3	3.66/133.94
14-H_3/C12	3.66/151.0	14-H_3/C12	3.66/151.09
–	–	14-H_3/C4	3.66/104.87
15-H_3/C10	3.57/162.6	15-H_3/C10	3.57/162.71
15-H_3/C12	3.57/151.0	15-H_3/C12	3.57/151.09
N–H/**C1**	12.73/129.7	N–H/**C4a**	12.72/129.76
N–H/C9a	12.73/136.8	N–H/C9a	12.72/136.74
N–H/C8	12.73/111.9	–	–
N–H/C8a	12.73/143.5	N–H/C8a	12.72/143.60
–	–	N–H/C4b	12.72/122.91

[a] Signals marked in bold have not been assigned correctly before[6] and have now been revised as shown.

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(11) **Spectroscopic Data for 2,4-Dimethyl-4,7-dihydro-1*H*-pyrimido[4,5-*c*]carbazole-1,3(2*H*)-dione (13)**
Light yellow solid; mp 307–309 °C. UV (MeOH): λ = 217, 257, 275 (sh), 334, 374, 392 nm. Fluorescence (MeOH): λ_{ex} = 257 nm, λ_{em} = 434, 518 nm. IR (ATR): ν = 3278, 3045, 2951, 2921, 2056, 2030, 2009, 1734, 1688, 1631, 1582, 1517, 1489, 1458, 1418, 1345, 1317, 1288, 1222, 1184, 1139, 1079, 1025, 987, 924, 862, 791, 742, 721, 698, 637, 606 cm^{-1}. ^1H NMR (500 MHz, C_5D_5N): δ = 3.56 (s, 3 H), 3.65 (s, 3 H), 7.32 (d, *J* = 8.9 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 1 H), 7.60 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1 H), 7.73 (d, *J* = 8.1 Hz, 1 H), 7.98 (d, *J* = 8.9 Hz, 1 H), 10.27 (d, *J* = 8.4 Hz, 1 H), 12.90 (br s, 1 H). ^{13}C NMR (125 MHz, C_5D_5N): δ = 28.71 (CH_3), 31.73 (CH_3), 110.96 (C), 111.45 (CH), 112.49 (CH), 118.68 (CH), 119.26 (CH), 120.91 (C), 123.20 (C), 127.29 (CH), 129.22 (CH), 136.28 (C), 137.32 (C), 142.72 (C), 151.07 (C=O), 162.83 (C=O). MS (70 eV): *m/z* (%) = 279 (100) [M^+], 222 (12), 221 (6), 194 (22), 193 (30), 167 (8), 166 (12), 139 (7). HRMS: *m/z* calcd for $C_{16}H_{13}N_3O_2$ [M^+]: 279.1008; found: 279.0999.

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(13) **Spectroscopic Data for Antipathine A {1,3-Dimethyl-1*H*-pyrimido[5,4-*b*]carbazole-2,4(3*H*,6*H*)-dione} (2)**
Yellow solid; mp 342–344 °C. UV (MeOH): λ = 219, 260, 318 (sh), 327, 383, 398 nm. Fluorescence (MeOH): λ_{ex} = 260 nm, λ_{em} = 448 nm. IR (ATR): ν = 3263, 3028, 2921, 2846, 1771, 1735, 1717, 1686, 1626, 1559, 1540, 1518, 1456, 1432, 1377, 1333, 1307, 1241, 1191, 1146, 1098, 1067, 1017, 965, 856, 834, 765, 742, 723, 706, 640 cm^{-1}. ^1H NMR (500 MHz, C_5D_5N): δ = 3.57 (s, 3 H), 3.66 (s, 3 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.66 (d, *J* = 8.2 Hz, 1 H), 8.14 (s, 1 H), 8.41 (d, *J* = 7.8 Hz, 1 H), 8.65 (s, 1 H), 12.72 (br s, 1 H). ^{13}C NMR (125 MHz, C_5D_5N): δ = 28.51 (CH_3), 31.03 (CH_3), 104.87 (CH), 110.19 (CH), 112.03 (CH), 114.50 (C), 119.62 (CH), 122.18 (CH), 122.91 (C), 128.46 (CH), 129.76 (C), 133.94 (C), 136.74 (C), 143.60 (C), 151.09 (C=O), 162.71 (C=O). MS (70 eV): *m/z* (%) = 279 (100) [M^+], 222 (10), 221 (5), 194 (18), 193 (36), 192 (5), 167 (10), 166 (12), 139 (7). HRMS: *m/z* calcd for $C_{16}H_{13}N_3O_2$ [M^+]: 279.1008; found: 279.1001.

(14) For the use of carbonyl groups as directing groups in palladium(II)-catalysed C–H functionalisations, see for example: (a) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (d) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (e) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 5524. (f) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864. (g) Gensch, T.; Rönnefahrt, M.; Czerwonka, R.; Jäger, A.; Kataeva, O.; Bauer, I.; Knölker, H.-J. *Chem. Eur. J.* **2012**, *18*, 770.