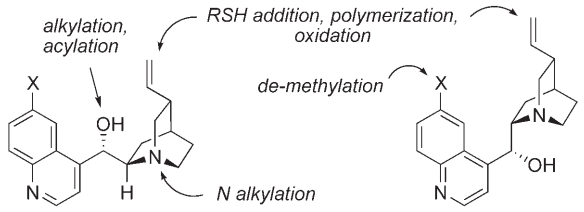
Synthetic Methods

DOI: 10.1002/anie.200701341

Nucleophilic Addition of Organometallic Reagents to Cinchona Alkaloids: Simple Access to Diverse Architectures**

Lukas Hintermann, Marco Schmitz, and Ulli Englert*

Cinchona alkaloids, with their fascinating structures and long-standing medicinal tradition, continue to attract the attention of organic chemists.[1] These compounds have played a prominent role in the study of stereochemistry[2] and the development of asymmetric catalysis.[3,4] Modification of the structure of the catalyst is a key factor when optimizing and fine-tuning the performance of a catalytic reaction. Modifications of cinchona alkaloids are mostly confined to a few reactive positions (Scheme 1),[3a] but changes to the carbon skeleton tend to be laborious.[1c,5,6] We now describe a simple and surprising derivatization of the core of cinchona alkaloids by the stereoselective 1′,4′-nucleophilic aromatic addition of Grignard reagents. Taken together with the complementary 1′,2′-addition of organolithium reagents,[7] core-modified cinchona alkaloid derivatives with rigid and tunable structures are readily available; such compounds are of interest as potential catalysts and supramolecular building blocks.

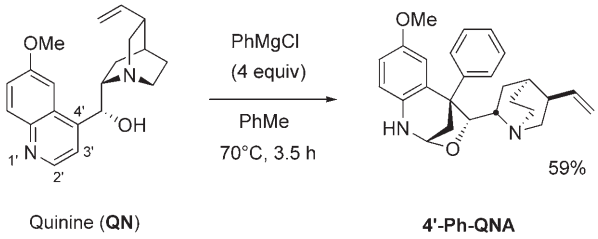


X = H: Cinchonine (**CN**) X = H: Cinchonidine (**CD**)

X = OMe: Quinidine (**QD**) X = OMe: Quinine (**QN**)

Scheme 1. Cinchona alkaloids and typical sites of modification.

The reaction of quinine with an excess of phenylmagnesium chloride in toluene results what spectroscopic data reveal is the formal addition product of C_6H_6 to the alkaloid. The structure **4′-Ph-QNA** (Scheme 2)[8] is in line with these observations, and was further confirmed by X-ray crystallographic analysis (Figure 1). This structure shows that a conjugate addition of the organometallic reagent to the heteroaromatic core and ring closure to an aminal had taken place.



Scheme 2. The reaction of quinine with a Grignard reagent.

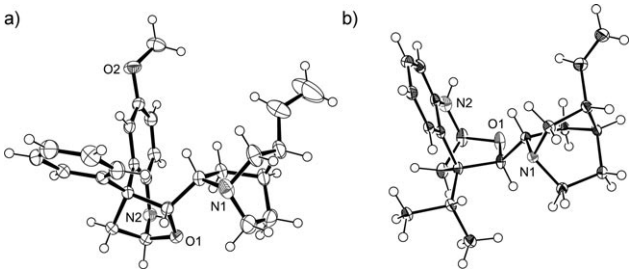


Figure 1. X-ray crystallographic structure determination of two aminals: a) **4′-Ph-QNA** and b) **4′-*i*Pr-CDA**.[8,10]

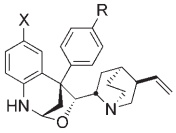
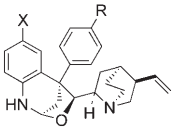
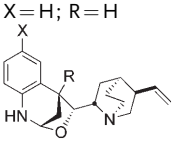
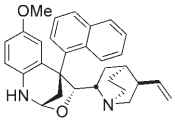
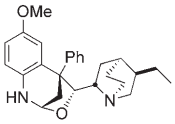
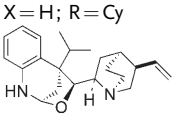
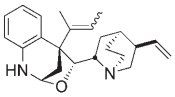
Cinchona alkaloid derivatives with extended rigid carbon frameworks incorporating reactive amine functional groups should be interesting candidates for applications as structurally tunable chiral catalysts, provided their synthesis is sufficiently general; which is indeed the case here: All four major cinchona alkaloids and a dihydro derivative react with Grignard reagents to give aminals as single diastereoisomers in satisfactory yields (Table 1).[9] Aryl Grignard reagents with either electron-donating or -accepting groups were readily transferred (Table 1, entries 3–5), including the bulky 1-naphthyl group (Table 1, entry 7). Primary and secondary alkyl groups were also added to the quinoline nucleus to give aminals (Table 2, entries 1–6), as was an alkenyl group (Table 1, entry 17). Very bulky nucleophiles (entry 15) afforded the 2′-alkylated alkaloid as the major product instead (Table 2, entry 1). The structure of the aminal **4′-*i*Pr-CDA** was also determined by X-ray crystallography (Figure 1).[10] Surprisingly, the substituent at the 4′-carbon

[*] Dr. L. Hintermann, Dipl.-Chem. M. Schmitz
Institut für Organische Chemie
RWTH Aachen
Landoltweg 1, 52074 Aachen (Germany)
Fax: (+49) 241-80-92391
E-mail: lukas.hintermann@oc.rwth-aachen.de
Prof. Dr. U. Englert
Institut für Anorganische Chemie
RWTH Aachen
Landoltweg 1, 52074 Aachen (Germany)

[**] This work was supported by the DFG (Emmy Noether Programm, SPP 1179 Organokatalyse). We thank Prof. Carsten Bolm for continued support and Chininfabrik Buchler GmbH, Braunschweig, for alkaloid samples.

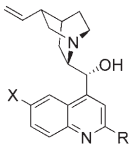
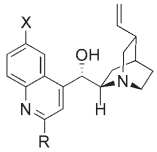
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Conjugate arylation of cinchona alkaloids with Grignard reagents.

Entry	SM[a]	Reagent[b] (equiv)	Product	Yield [%]	Entry	SM[a]	Reagent[b] (equiv)	Product	Yield [%]
									
1	**QN**	PhMgBr (3)	X = OMe, R = H	35	9	**QD**	PhMgBr (5)	X = OMe; R = H	53
2	**QN**	PhMgCl (4)	X = OMe, R = H	59	10	**CN**	PhMgBr (5)	X = H; R = H	65
3	**QN**	*p*-MeC_6H_4MgBr (5)	X = OMe, R = Me	59	11	**QN**	MeMgCl (8)		62
4	**QN**	*p*-ClC_6H_4MgBr (5)	X = OMe; R = Cl	51					
5	**QN**	*p*-$MeOC_6H_4MgBr$ (5)	X = OMe; R = OMe	55					
6	**CD**	PhMgBr (3)	X = H; R = H	80	12	**QN**	EtMgBr (6)	X = OMe; R = Et	51
7	**QN**	1-NapMgBr (5)[d]		32	13	**CD**	*n*-$C_{10}H_{21}MgCl$ (3.5)	X = H; R = n-$C_{10}H_{21}$	35
					14	**CD**	*i*PrMgCl (4)	X = H; R = *i*Pr	35
8	**DHQN**[c]	PhMgBr (5)		63	15	**CD**	CyMgCl (6)	X = H; R = Cy	5[e]
					16	**CN**	*i*PrMgCl (8)		53
					17	**CD**			42[f]

[a] Starting material. [b] Reactions were performed in toluene at 50–70 °C for 1 h to 1 day.[9] Cy = cyclohexyl. [c] DHQN = dihydroquinine. [d] 1-Nap = 1-naphthyl. [e] **2′-Cy-CD** is the main reaction product (43 %), see Table 2. [f] *E*/*Z* = 70:30.

Table 2: Alkylation of cinchona alkaloids at the 2′-position.

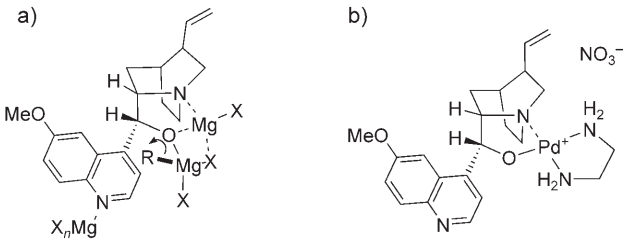
Entry	SM[a]	Reagent[b] (equiv)	Product	Yield [%]
				
1	**CD**	CyMgCl (6)	X = H, R = Cy	43
			+ **4′-Cy-CDA**	5
2	**CD**	iPr_2Mg (1.9)	X = H, R = *i*Pr	29
3	**CD**	BnMgBr (6)	X = H, R = Bn	35
4	**CD**	NapMgBr (3.6)	X = H, R = 1-Nap	17
5	**CD**	*n*BuLi (3)	X = H, R = *n*Bu	66
6	**CD**	PhLi (3)	X = H, R = Ph	27
7	**QN**	*n*BuLi (3)	X = OMe, R = *n*Bu	37
8	**QN**	PhLi (3)	X = OMe, R = Ph	32
				
9	**CN**	*n*BuLi (2.1)	X = H, R = Bu	55
10	**CN**	UdcLi (2.5)[c]	X = H, R = Udc	48
11	**CN**	PhLi (2.2)	X = H, R = Ph	7[d]

[a] Starting material. [b] Conditions with RLi: *t*BuOMe, −20 °C–RT, 3 h; workup with H_2O, HOAc, and I_2 or MnO_2. Conditions with RMgX: PhMe/ethereal solvent, 65–90 °C, 5–20 h.[9] [c] Udc = *n*-undec-10-en-1-yl. [d] Without oxidative workup.

atom of the alkaloid decisively influences the conformation of the resulting aminals: The dihedral angle O-C-C-N (around the bond joining the quinuclidine and bicyclic aminal fragments) amounts to 96° in **4′-Ph-QNA**, but to 179° (or 175°) in **4′-*i*Pr-CDA**,[11] which implies that the conformation of the cinchona aminals can be adjusted by choice of the group that is introduced at the C-4′-position.

Notably, the organometallic reagent adds to the sterically less available 4′-position of the quinoline moiety rather than at the C-2′-position, and single diastereoisomers were isolated from all reactions. Both observations are explained by assuming a group transfer within a chelate (Scheme 3a)[12] having the same quinoline conformation as observed earlier in a metal complex of quinine (Scheme 3b).[13] The choice of toluene as a solvent that will not break up aggregates is a key factor for obtaining good results in the conjugate addition.

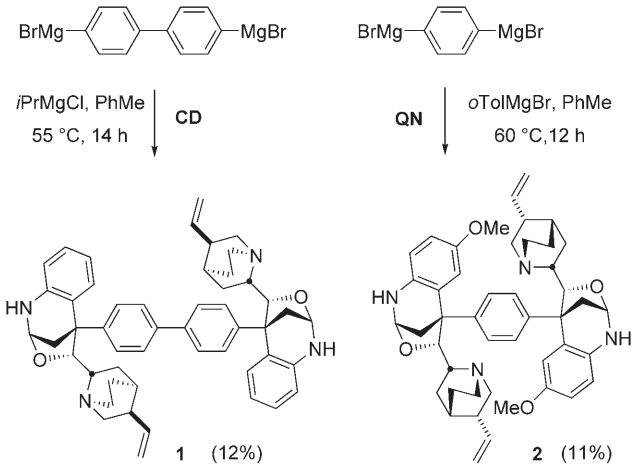
The 4′-addition was accompanied or overturned by 2′-substitution with bulky Grignard reagents (Table 2, entries 1–4). 1-Naphthylmagnesium bromide afforded either 4′- (Table 1, entry 7) or 2′-alkylation products (Table 2, entry 4), depending on the reaction conditions. If 2′-



Scheme 3. a) Mechanistic description of a chelate-directed transfer of an R group from RMgX to the quinoline unit. b) Structure of a metal–chelate complex of quinine.[13]

alkylation is desired, organolithium nucleophiles are advantageous:[7] After an oxidative workup, C-2′-substituted alkaloids were obtained in fair yields (Table 2, entries 5–11).

Direct alkylation of the core of cinchona alkaloids with organometallic reagents opens the way to assemble complex molecular architectures in a predictable manner: for example, the fascinating dinuclear derivatives **1** and **2** (Scheme 4) were obtained from divalent Grignard reagents.[14]

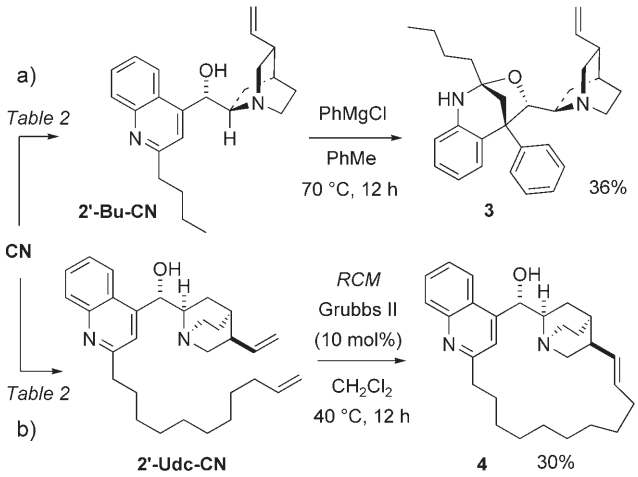


Scheme 4. Dinuclear arylene-bridged alkaloid derivatives. *o*Tol = *ortho*-tolyl.

Structural diversity is further enhanced by performing serial 2′- and 4′-alkylations, as in the synthesis of **3** (Scheme 5a). Another notable reaction sequence has introduced the unsaturated 10-undecenyl chain by 1′,2′-addition, followed by ring-closing metathesis to give cycloalkaloid **4** (Scheme 5b).[15]

In conclusion, simple modifications of the basic carbon skeleton of cinchona alkaloids are rare, but we have now found that the direct nucleophilic alkylation of organometallic reagents provides a powerful tool to access structurally diverse derivatives with rigid cores that bear reactive functional groups. Such derivatives are of interest for applications in organo or metal catalysis; last but not least, the surprising course of the reaction of Grignard reagents with cinchona alkaloids has been elucidated, and has yielded an unexpected result.[9]

Received: March 27, 2007
Published online: May 30, 2007



Scheme 5. Structural diversity from cinchona alkaloids by alkylative reaction sequences. RCM = ring-closing metathesis.

Keywords: cinchona alkaloids · Grignard reaction · heterocycles · neighboring-group effects · nucleophilic addition

[1] a) J. I. Seeman, *Angew. Chem.* **2007**, *119*, 1400–1435; *Angew. Chem. Int. Ed.* **2007**, *46*, 1378–1413; b) T. S. Kaufman, E. A. Rúveda, *Angew. Chem.* **2005**, *117*, 876–907; *Angew. Chem. Int. Ed.* **2005**, *44*, 854–885; c) H. M. R. Hoffmann, J. Frackenpohl, *Eur. J. Org. Chem.* **2004**, 4293–4312; d) R. Verpoorte, J. Schripsema, T. van der Leer, *Alkaloids* **1988**, *34*, 331–398.

[2] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 954.

[3] a) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961–998; b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; c) H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87–129; d) H. Pracejus, *Fortschr. Chem. Forsch.* **1967**, *8*, 493–553.

[4] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.

[5] Alkaloid functionalization by C–C bond formation at the vinyl group: a) M. P. Arrington, Y. L. Bennani, T. Göbel, P. Walsh, S.-H. Zhao, K. B. Sharpless, *Tetrahedron Lett.* **1993**, *34*, 7375–7378; b) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229–8243; c) W. M. Braje, J. Frackenpohl, O. Schrake, R. Wartchow, W. Beil, H. M. R. Hoffmann, *Helv. Chim. Acta* **2000**, *83*, 777–792; d) F. Fache, O. Piva, *Tetrahedron Lett.* **2001**, *42*, 5655–5657; e) M. Lambers, F. H. Beijer, J. M. Padron, I. Toth, J. G. de Vries, *J. Org. Chem.* **2002**, *67*, 5022–5024; f) A. Merschaert, P. Delbeke, D. Daloze, G. Dive, *Tetrahedron Lett.* **2004**, *45*, 4697–4701.

[6] Alkaloid derivatization by C–C bond formation at the C-2′-position: a) J. F. Mead, M. M. Rapport, J. B. Koepfli, *J. Am. Chem. Soc.* **1946**, *68*, 2704–2705; b) E. Ochiai, M. Hamana, Y. Kobayashi, C. Kaneko, *Chem. Pharm. Bull.* **1960**, *8*, 487–490; c) E. Ochiai, H. Kataoka, T. Dodo, H. Tanida, M. Horiuchi, R. Kido, *Chem. Abstr.* **1961**, 106009; d) J. P. Yardley, R. E. Bright, L. Rane, R. W. A. Reeks, P. B. Russell, H. Smith, *J. Med. Chem.* **1971**, *14*, 62–65; e) J. P. Yardley, R. E. Bright, R. W. Rees, H. Smith, US Pat. 3663552, **1972**; f) W. A. Laurie, D. McHale, K. Saag, J. B. Sheridan, *Tetrahedron* **1988**, *44*, 5905–5910; g) R. A. Daines, WO 9709046, **1997**.

[7] Direct 1′,2′-addition of PhLi to quinine: a) Ref. [6a]; b) addition of RLi to O-alkylated alkaloids: C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith, M. J. Gaunt, *Angew.*

Chem. **2006**, *118*, 6170 – 6174; *Angew. Chem. Int. Ed.* **2006**, *45*, 6024 – 6028.

[8] **4′-Ph-QNA** corresponds to the aminal product of addition of PhMgX to the C-4′-position of the alkaloid (**QN**).

[9] See the Supporting Information for experimental details and characterization of the reaction products.

[10] CCDC-639151 (**4′-*i*Pr-CDA**) and -639152 (**4′-Ph-QNA**) 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] The conformational difference is retained in $CDCl_3$ solution, as evident from a shielded H NMR signal for H-14 in the spectrum of **4′-Ph-QNA**, which is absent for **4′-*i*Pr-CDA**. The two torsion angles correspond to independent molecular units within the asymmetric cell.

[12] Metal-directed transfer of hydride to C-4′ of cinchona alkaloids: H. M. R. Hoffmann, T. Plessner, C. von Riesen, *Synlett* **1996**, 690 – 692.

[13] R. Hubel, K. Polborn, W. Beck, *Eur. J. Inorg. Chem.* **1999**, 471 – 482.

[14] Since an excess of divalent Grignard reagent favors mononuclear reaction products, the yields are low, even though the reactions were performed in the presence of excess "dummy" Grignard reagent (*i*PrMgCl or *o*TolMgBr).

[15] Only the *E* isomer was isolated; for the cyclization protocol, see: A. Fürstner, K. Langemann, *Synthesis* **1997**, 792 – 803.

