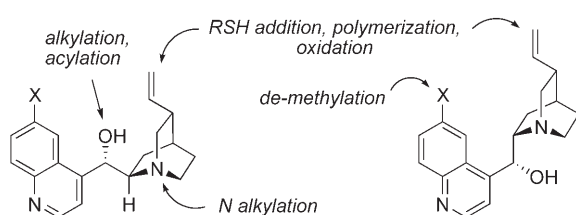


Nucleophilic Addition of Organometallic Reagents to Cinchona Alkaloids: Simple Access to Diverse Architectures**

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



X = H: Cinchonine (CN)

X = H: Cinchonidine (CD)

X = OMe: Quinidine (QD)

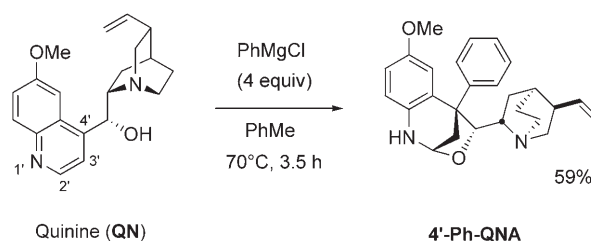
X = OMe: Quinine (QN)

Scheme 1. Cinchona alkaloids and typical sites of modification.

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.

The reaction of quinine with an excess of phenylmagnesium chloride in toluene results what spectroscopic data

reveal is the formal addition product of C₆H₆ 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.

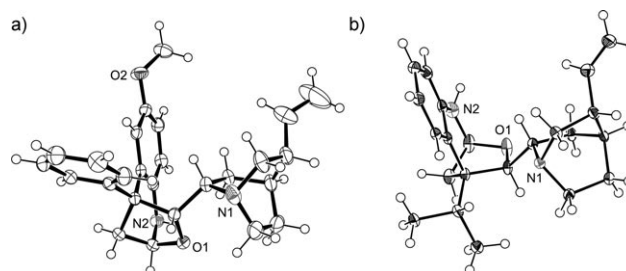


Figure 1. X-ray crystallographic structure determination of two amins: a) **4'-Ph-QNA** and b) **4'-iPr-CDA**.^[8,10]

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 amins 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 amins (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'-iPr-CDA** was also determined by X-ray crystallography (Figure 1).^[10] Surprisingly, the substituent at the 4'-carbon

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[**] 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	<i>p</i> -MeC ₆ H ₄ MgBr (5)	X = OMe, R = Me	59	11	QN	MeMgCl (8)	X = H; R = H	62
4	QN	<i>p</i> -ClC ₆ H ₄ MgBr (5)	X = OMe; R = Cl	51					
5	QN	<i>p</i> -MeOC ₆ H ₄ MgBr (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	<i>n</i> -C ₁₀ H ₂₁ MgCl (3.5)	X = H; R = <i>n</i> -C ₁₀ H ₂₁	35
					14	CD	<i>i</i> PrMgCl (4)	X = H; R = <i>i</i> Pr	35
8	DHQN ^[c]	PhMgBr (5)		63	15	CD	CyMgCl (6)	X = H; R = Cy	5 ^[e]
					16	CN	<i>i</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 + 4'-Cy-CDA	43 5
2	CD	<i>i</i> Pr ₂ Mg (1.9)	X = H, R = <i>i</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	<i>n</i> BuLi (3)	X = H, R = <i>n</i> Bu	66
6	CD	PhLi (3)	X = H, R = Ph	27
7	QN	<i>n</i> BuLi (3)	X = OMe, R = <i>n</i> Bu	37
8	QN	PhLi (3)	X = OMe, R = Ph	32
9	CN	<i>n</i> 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]

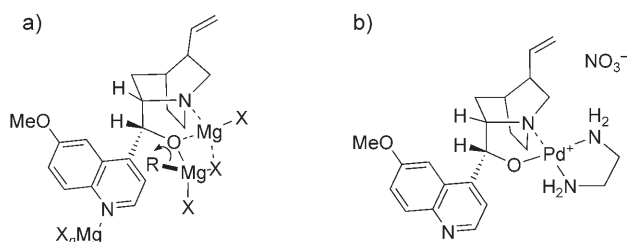
[a] Starting material. [b] Conditions with RLi: *t*BuOMe, –20 °C–RT, 3 h; workup with H₂O, HOAc, and I₂ or MnO₂. Conditions with RMgX: PhMe/etheral solvent, 65–90 °C, 5–20 h.^[9] [c] Udc = *n*-undec-10-en-1-yl. [d] Without oxidative workup.

atom of the alkaloid decisively influences the conformation of the resulting amins: The dihedral angle O–C–C–N (around the bond joining the quinuclidine and bicyclic aminal frag-

ments) amounts to 96° in **4'-Ph-QNA**, but to 179° (or 175°) in **4'-iPr-CDA**,^[11] which implies that the conformation of the cinchona amins 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 quino-line 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.

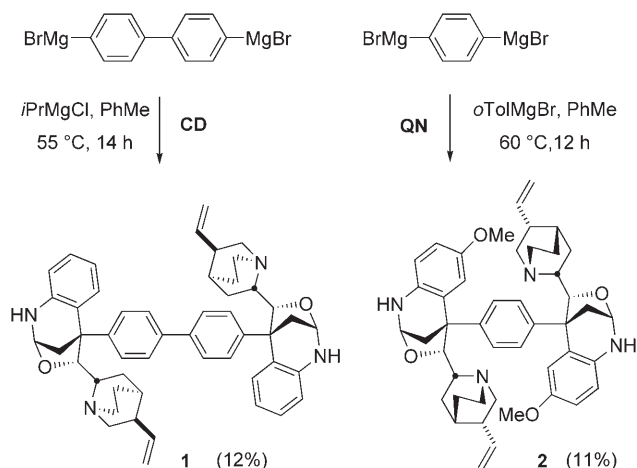
The 4'-addition was accompanied or overturned by 2'-substitution with bulky Grignard reagents (Table 2, entries 1–4). 1-Naphthylmagnesium bromide afforded either 4'- (Table 1, entry 7) or 2'-alkylation products (Table 2, entry 4), depending on the reaction conditions. If 2'-



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]

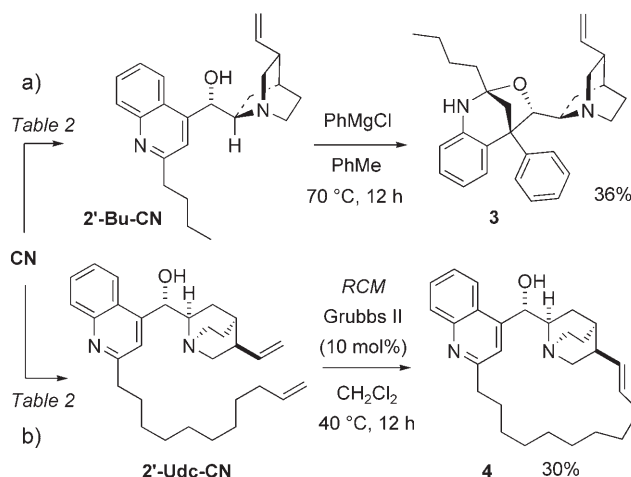


Scheme 4. Dinuclear arylene-bridged alkaloid derivatives. *o*Tol = *ortho*-tolyl.

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

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