Phase-Transfer Catalysis

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Discovery and Application of Doubly Quaternized Cinchona-Alkaloid-Based Phase-Transfer Catalysts**

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Dedicated to Ulf-H. Dolling and Edward J. J. Grabowski on the 30th anniversary of their first report of an asymmetric alkylation under phase-transfer catalysis

Abstract: *We report the discovery of novel N,N′-disubstituted cinchona alkaloids as efficient phase-transfer catalysts for the assembly of stereogenic quaternary centers. In comparison to traditional cinchona-alkaloid-based phase-transfer catalysts, these new catalysts afford substantial improvements in enantioselectivity and reaction rate for intramolecular spirocyclization reactions with catalyst loadings as low as 0.3 mol% under mild conditions.*

Asymmetric phase-transfer catalysis has been established as a powerful, yet practical method for challenging enantioselective transformations, and is of great relevance to the industrial application of green chemistry.[1] The first industrial-scale asymmetric alkylation reaction, mediated by a cinchona-alkaloid-based phase-transfer catalyst (PTC), was reported in 1984 by Merck for the construction of the stereogenic quaternary carbon center in **2** with remarkable enantioselectivity (92% *ee*; Scheme 1).[2,3] Since then, cinchona-alkaloid-based PTCs have been applied to many practical asymmetric syntheses in both academic and industrial settings.[4] The structures of cinchona-alkaloid-based PTCs have been modified by functionalization of the C9 hydroxy group or quaternization of the bridgehead amine; however, to our knowledge, there are no examples of PTCs in which the quinoline nitrogen was also quaternized. Herein, we report the discovery of *N,N′*-disubstituted cinchona alkaloids, wherein both the quinuclidine nitrogen (*N*) and the quinoline nitrogen (*N′*) are quaternized, as a new generation of phase-transfer catalysts.

During our studies directed toward the practical synthesis of calcitonin gene-related peptide (CGRP) antagonist candidates MK-8825 and MK-3207 for the treatment of migraines (Figure 1),[5] we again faced the challenge of developing an enantioselective synthesis of a stereogenic quaternary carbon center, this time in a 3,3-spiro-7-azaoxindole. Although this and related structural motifs are common in both naturally derived and biologically active compounds,[6] there have been few reports of their preparation by practical asymmetric synthesis, despite numerous developments in the field of phase-transfer catalysis.[7]

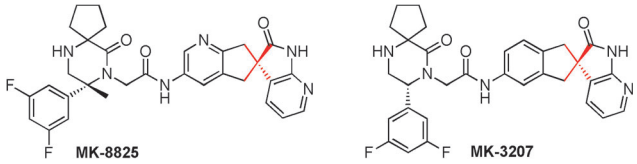
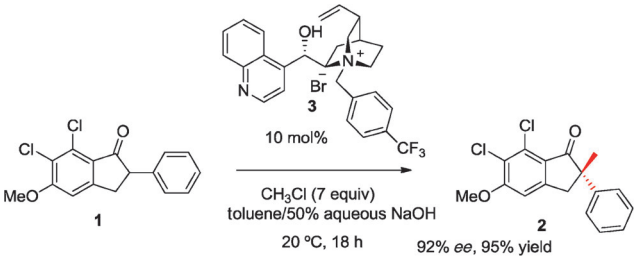
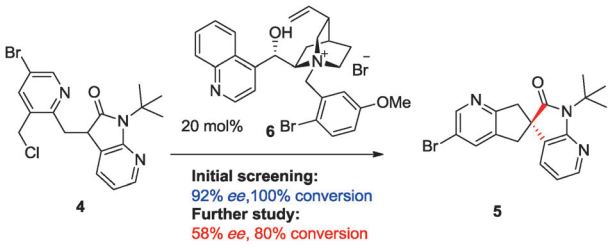


Figure 1. CGRP-antagonist candidates for the treatment of migraines.



Scheme 1. The first industrial application of an asymmetric PTC at Merck.

Among several synthetic routes we evaluated, the spirocyclization of benzyl chloride **4** under phase-transfer catalysis was the most attractive for constructing the stereogenic quaternary center in MK-8825 (Scheme 2). Unfortunately,



Scheme 2. Initial screening of the asymmetric alkylation. Screening conditions: **4** (1 mg) in toluene (0.075 mL, 0.027 M), NaOH (0.025 mL, 0.3 N), 0 °C, PTC (20 mol%), 19 h.

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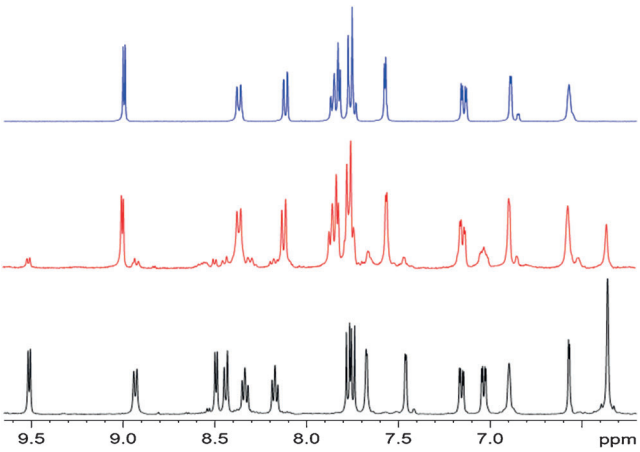
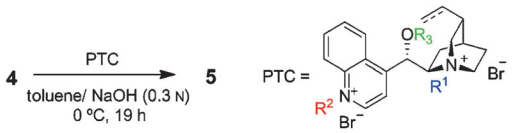


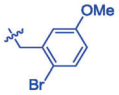
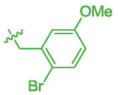
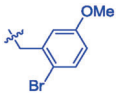
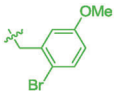
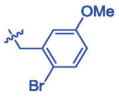
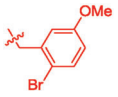
Figure 2. Comparison of the ^{1}H NMR spectra of **6** and **9a** in [D$_6$]dimethyl sulfoxide (blue: pure **6**; red: original batch of **6**; black: **9a**).

a majority of phase-transfer catalysts examined in the spirocyclization of **4** did not show complete conversion after 19 h, and the enantioselectivity was generally modest.[8] However, we observed unique results with PTC **6**, which afforded the desired product **5** in high yield with 92% *ee*.

As new batches of PTC **6** were prepared for the demonstration of this reaction on a larger scale, we were surprised to find that the reaction proceeded at a slower rate (80% conversion, 19 h) and with lower enantioselectivity (58% *ee*) than results in our initial screening. A ^{1}H NMR spectrum of the batch of PTC **6** used in the original screen revealed several significant impurities (Figure 2). We speculated that the unknown components were generated during the preparation of **6** by overalkylation of the cinchona alkaloid. After extensive NMR spectroscopic analysis, we were able to conclude that no *O*-alkylated impurities were present; however, evidence supporting a quaternized quinoline nitrogen was inconclusive. To understand the reactivity of these hypothesized compounds, we independently prepared and screened each as a catalyst in the spirocyclization of **4** (Table 1). We found that catalyst **9a**, a unique cinchona alkaloid containing both a quaternized quinuclidine nitrogen and a quaternized quinoline nitrogen,[9] afforded results that were consistent with those observed in the original reac-

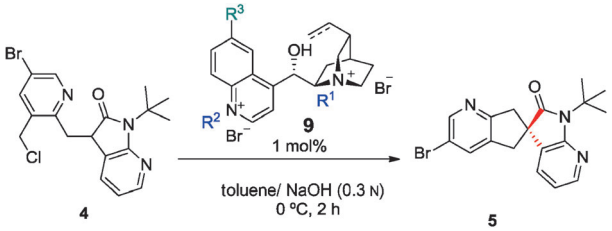
Table 1: Introduction of additional functional groups on the PTC.

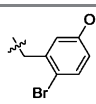
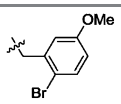
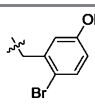
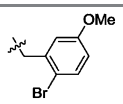
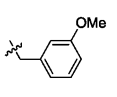
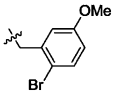
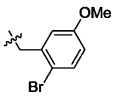
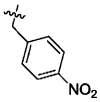
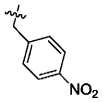
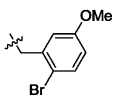


PTC	R^1	R^2	R^3	*ee* [%]	Conv. [%]
6[a]		none	H	58	80
7[a]	none	none		34	90
8[a]		none		67	80
9a[b]			H	92	100[c]

[a] PTC: 20 mol%. [b] PTC: 1 mol%. [c] The reaction was complete within 1 h.

Table 2: Selected results from the screening of doubly quartenized phase-transfer catalysts.



	Cinchonine series (R^3 = H)				Quinidine series (R^3 = OMe)			
PTC	R^1	R^2	*ee* [%]	PTC	R^1	R^2	*ee* [%]
9a			92	**9g**			94
9b			78	**9h**			89
9c[a]		Me	80	**9i**			84
9d			47	**9j**			90
9e	allyl		70	**9k**[b]			46
9f			42	**9l**			67
				9m[b]			81

[a] Mixed Br$^-$/I$^-$ salt. [b] Catalysts **9k** and **9m** are the dihydroquinidine derivatives.

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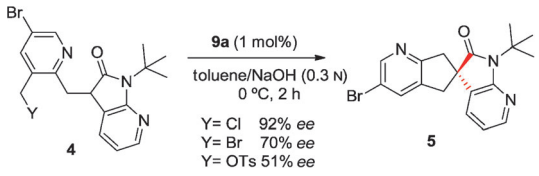
tion. Moreover, PTC **9a** exhibited a remarkable rate acceleration in the spirocyclization and afforded complete conversion at only 1 mol% loading in 1 h (92% *ee*). Complete conversion was not observed with the other catalysts even at 20 mol% loading after 19 h.

Owing to the improved reactivity and enantioselectivity observed with the *N*,*N*′-doubly quaternized cinchona-alkaloid-based catalyst **9a**, a collection of similar catalysts was prepared with different substituents at *N* and *N*′, and each was examined in the spirocyclization of **4** (Table 2).[10] In every case, *N*′-quaternization accelerated the reaction, resulting in 100% conversion within 2 h at 1 mol% loading. *N*,*N*′-Doubly quaternized cinchona-alkaloid-based catalysts generally demonstrated improved enantioselectivity in the spirocyclization versus the traditional cinchona-alkaloid-based phase-transfer catalysts. In fact, the introduction of even a methyl group at the *N*′ position dramatically improved the enantioselectivity (**9c**; 80% *ee*). Although the best enantioselectivities in the spirocyclization of **4** were observed with catalysts containing a 2-bromo-5-methoxybenzyl substituent as R^1, respectable selectivities could be achieved with other R^1 substituents by modification of the cinchona-alkaloid scaffold and/or the R^2 substituent (**9e** and **9m**). The effect of changes to the counterion on both rate and enantioselectivity was minor. For example, with catalyst **9a**, the bis-bromide, bis-iodide, and mixed salts all provided the product with 90% *ee*.

The impact of the leaving group in **4** on the stereochemical course of the reaction was studied (Scheme 3). Consistent with the observations of Dolling et al., when the leaving group was changed from a chloride to either a bromide or a tosylate (OTs) group, the enantioselectivity of the spirocyclization decreased significantly.[2,11]

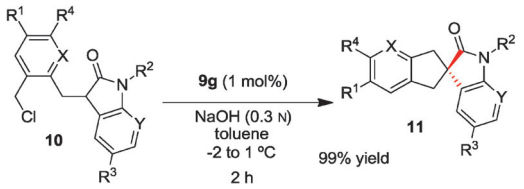


Scheme 3. Effect of the leaving group.

To explore the potential of these novel catalysts, several structurally related substrates were synthesized and evaluated under similar spirocyclization conditions. In general, the reactions proceeded smoothly in consistently high yield with varying levels of enantioselectivity (Table 3). Various functional groups at the C3 position of the pyridine ring (**10a–c**) were well-tolerated; however, the replacement of the pyridine ring with a substituted phenyl group led to a significant decrease in the enantioselectivity (**10h**). In contrast, both azaindoline and indoline substrates provided similar levels of enantioselectivity (**10a** versus **10e**). Notably, modification of the R^2 substituent (**10e–g**) had a profound effect on the enantioselectivity, whereby a *tert*-butyl substituent consistently afforded the highest level of selectivity.

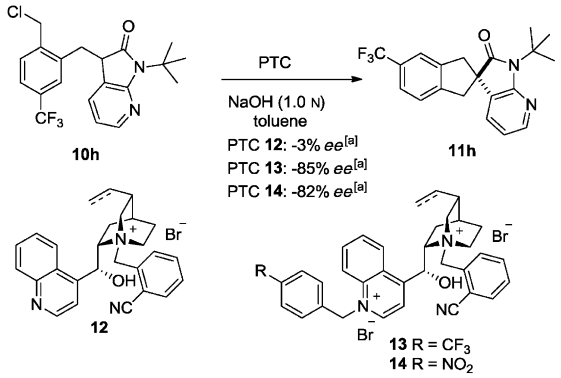
With three structural components that can be independently modified (the cinchona-alkaloid core, the *N*-substituent, and the *N*′-substituent), there is tremendous opportunity to optimize the catalyst for each substrate. For example, the enantioselectivity in the spirocyclization of **10h** in Table 3 (56% *ee*) was improved to 85% *ee* by changing the cinchona-alkaloid core from cinchonine to cinchonidine (Scheme 4).[12] The traditional cinchona-alkaloid-based PTC **12**, which is not quaternized at *N*′, induced almost no enantioselectivity, thus highlighting the unique reactivity and selectivity of this new class of catalysts in enantioselective spirocyclization reactions under phase-transfer catalysis.

Table 3: Application of PTC **9g** to other substrates.



10	R^1	R^2	R^3	R^4	X	Y	11	*ee* [%]
10a	Cl	*t*Bu	H	H	N	N	**11a**	94
10b (**4**)	Br	*t*Bu	H	H	N	N	**11b** (**5**)	92
10c	CO_2Me	*t*Bu	H	H	N	N	**11c**	92
10d	Cl	*t*Bu	F	H	N	N	**11d**	96
10e	Cl	*t*Bu	H	H	N	CH	**11e**	90[a]
10f	Cl	Ph	H	H	N	CH	**11f**	85[a]
10g	Cl	Me	H	H	N	CH	**11g**	65[a]
10h	H	*t*Bu	H	CF_3	CH	N	**11h**	56[a]

[a] The absolute configuration was assigned by analogy to **5**.



Scheme 4. Optimization of the spirocyclization of **10h**. [a] The absolute configuration was assigned by analogy to **5**.

As a testament to the remarkable reactivity of this new class of catalysts, the loading of catalyst **9g** in the spirocyclization of **10a** was reduced to as low as 0.30 mol% with 1.1 equivalents of a weak base while still achieving 100% conversion in 3 h at about 0 °C, with no decrease in enantioselectivity (Scheme 5). This catalyst loading is unprecedented in reactions under cinchona-alkaloid phase-transfer catalysis, which usually require 10–20 mol% of the catalyst. Furthermore, the substrate concentration and stirring rate do not appear to have a significant effect on the reaction yield and *ee* value; thus, the reaction can be performed at high concentration with gentle agitation. Optimized conditions

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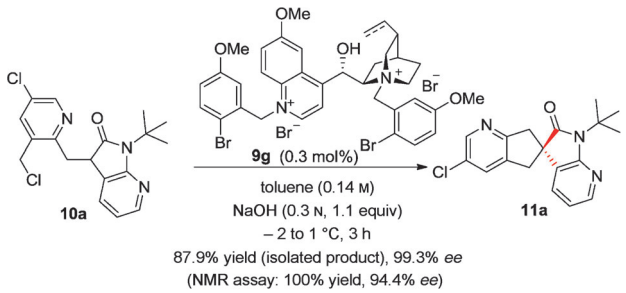

Scheme 5. Optimized asymmetric alkylation.

have been successfully applied at a large scale to demonstrate the robustness and practicality of this catalyst.

In summary, we have discovered a new class of cinchona-alkaloid-based phase-transfer catalysts, which are quaternized at both the quinuclidine nitrogen and the quinoline nitrogen. These catalysts demonstrate unprecedented reactivity and enantioselectivity in the spirocyclization of substrates such as compound **4**. The reaction is robust, mild, and environmentally friendly. These catalysts are readily prepared from commercially available cinchona alkaloids and alkyl halides, and preliminary experiments in our laboratories suggest that they may open new avenues in the area of asymmetric transformations. Detailed studies on the mechanism/kinetics of this catalysis and applications to other reactions will be reported in due course.

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Keywords: asymmetric synthesis · enantioselectivity · organocatalysis · phase-transfer catalysis · spiro compounds

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[8] Enantioselectivity of product **5** ranged from 0 to 58% *ee*. Selected results are presented in the Supporting Information for an initial cyclization with PTCs, including a Maruoka catalyst and dimeric monoquaternized cinchona-alkaloid catalysts developed by Park, Jew, and co-workers: a) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519; b) H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew, *Angew. Chem.* **2002**, *114*, 3162; *Angew. Chem. Int. Ed.* **2002**, *41*, 3036.
[9] Although studies have been reported on *N*,*N*′-doubly quaternized cinchona alkaloids, there is no precedent for their application as phase-transfer catalysts (references are listed in the Supporting Information).
[10] All of the *N*,*N*′-doubly quaternized cinchona-alkaloid-based catalysts were readily prepared from commercially available cinchona alkaloids in one or two steps. All cinchona alkaloids had a mixture of ethyl and vinyl functional groups at C3 of the quinuclidine moiety, unless specifically mentioned. We observed no difference in reactivity or enantioselectivity between **9g** with a mixture of ethyl and vinyl groups at C3 and the corresponding pure C3-ethyl-substituted compound **9g**.
[11] Recently, new calculated transition state modeling of the PTC including the leaving group effect was reported: E. de Freitas, J. R. Pliego, Jr., *ACS Catal.* **2013**, *3*, 613.
[12] Owing to the pseudoenantiomeric nature of cinchonidine with respect to cinchonine, the absolute configuration of product **11** was opposite to that of the product obtained with **9g**; A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem.* **1986**, *98*, 442; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 476.

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