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Amide-Based *Cinchona* Alkaloids as Phase-Transfer Catalysts: Synthesis and Potential Application

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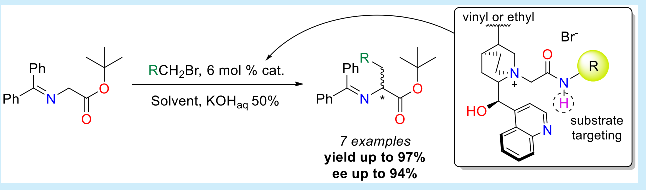
Supporting Information

ABSTRACT: Herein we present a library of simple amide derivatives of *Cinchona* alkaloids in the form of quaternary ammonium salts. The obtained derivatives can be generated very easily and efficiently from inexpensive and commercially available substrates. We tested this class of alkaloids in the alkylation of glycine derivative, carried out under phase-transfer catalyst conditions. The presented hybrid catalysts offer both high reaction yields (up to 97%) and high enantioselectivities of the obtained product (up to 94% ee).



Asymmetric catalytic synthesis remains a dynamically developing field of organic chemistry.[1,2] Stereoselective methods for forming carbon−carbon and carbon−heteroatom bonds using asymmetric catalysis have found wide applications not only in laboratory practice but also in industry,[3,4] giving rise to a continual demand for useful, biologically active synthetic compounds.[5] One of the most effective ways of introducing new stereogenic centers to create useful synthetic compounds involves organocatalysis, using molecules of natural origin as a source of chirality. The most important advantages of organocatalysis include simple and effective synthetic procedures that provide for mild reaction conditions, the possibility of easy rescaling, as well as the use of inexpensive and environmentally neutral reagents and solvents. Over the last two decades, phase-transfer catalysis (PTC)[6,7] has proven to be a methodology that offers exceptional properties, including in the practical sense. This approach has been widely used in recent years for many organic reactions, such as alkylation,[8] epoxidation,[9] Michael addition,[10] and so on.[6]

The choice of chiral catalyst is conditioned by a combination of three factors: its efficiency (its ability to provide high stereoselectivity), its availability, and also its cost, which is crucial for the economic viability of the project. Among the various catalytically active motifs, chiral quaternary ammonium salt catalysts are the most promising, and the development of new catalysts to facilitate a variety of different reactions has been thoroughly investigated by research groups all over the world.[11] The most commonly used chiral blocks understood in this way include *Cinchona* alkaloids,[12,13] amino acids,[14] sugars,[15] tartaric acid,[16] and certain synthetic chiral compounds, such as derivatives of 1,1′-binaphtol (BINOL)[6f] and *trans*-1,2-diaminocyclohexane (DACH).[17]

PTC catalysts' capacity for enantiodiscrimination crucially hinges upon ionic interactions. Such interactions, consisting of the formation of ionic pairs, do not provide for a defined stereochemical course of these reactions. A partial solution to this problem has arisen with the emergence of a new family of "hybrid" bifunctional catalysts, having both an ionic function and a fragment acting as a hydrogen bond donor.[18] Designing efficient hybrid catalysts requires that the catalyst architecture incorporates functions that facilitate directional interactions with reagents. Hydrogen bonds' directionality and range make them an excellent choice in the process of designing modern PTC catalysts. The hydroxyl, amide, and urea functions, in particular, serve as effective hydrogen bond "boosters" in this respect.

Herein we present a class of hybrid catalysts in the form of quaternary ammonium salts, based on *Cinchona* alkaloids, decorated with amide function. We expected the enantioselectivity of reactions carried out with these catalysts to be augmented due to the formation of strong, directional hydrogen bonds, resulting in the creation of the appropriate geometry of the resulting complex. The choice of substituent on the aromatic ring determines the strength and possibility of forming electrostatic interactions (including π-stacking) as well as the acidity of the amide proton and the strength of the hydrogen bonds formed.

A so-designed catalyst offers the opportunity to preorganize the substrate molecule, which, in turn, should allow for a precisely targeted nucleophile attack on the electrophilic object, as shown in Scheme 1: Panel a shows the model for one of the best catalysts, and panel b shows the model for one of the less selective catalysts. The presented models were generated on the basis of computer calculations using the density functional theory (DFT) method with global hybrid functional M06-2X, combined with the 6-31G* basis set.

To obtain a library of amide-based quaternary ammonium salts, we prepared α-bromoamides (**1**−**21**) appropriately substituted on the aromatic ring, generated from variously substituted anilines. A typical synthesis procedure for catalysts **22**−**43** is presented in Scheme 2 with their overall yields. In

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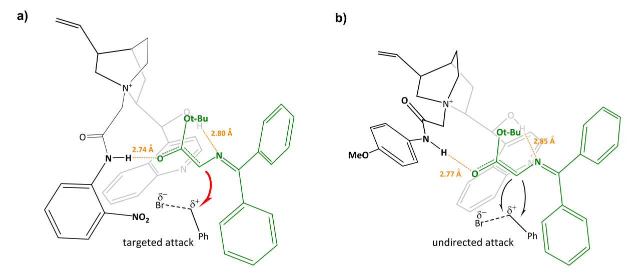
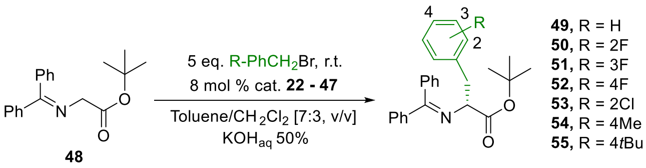
Scheme 1. Models Rationalizing the Enantioselectivity of *Cinchona*-Derived PTC Catalysts



Scheme 3. Benzylation of Imine 48 Using Catalysts 22−43[a]



[a]For example, Compound **49** was obtained using imine **48** (1.0 mmol), benzyl bromide (5.0 mmol), and catalyst **31** (8 mol %) in toluene/CH_2Cl_2 (7:3 v/v) (5 mL) and 50% aqueous KOH solution (3 mL) for 4 h at room temperature.

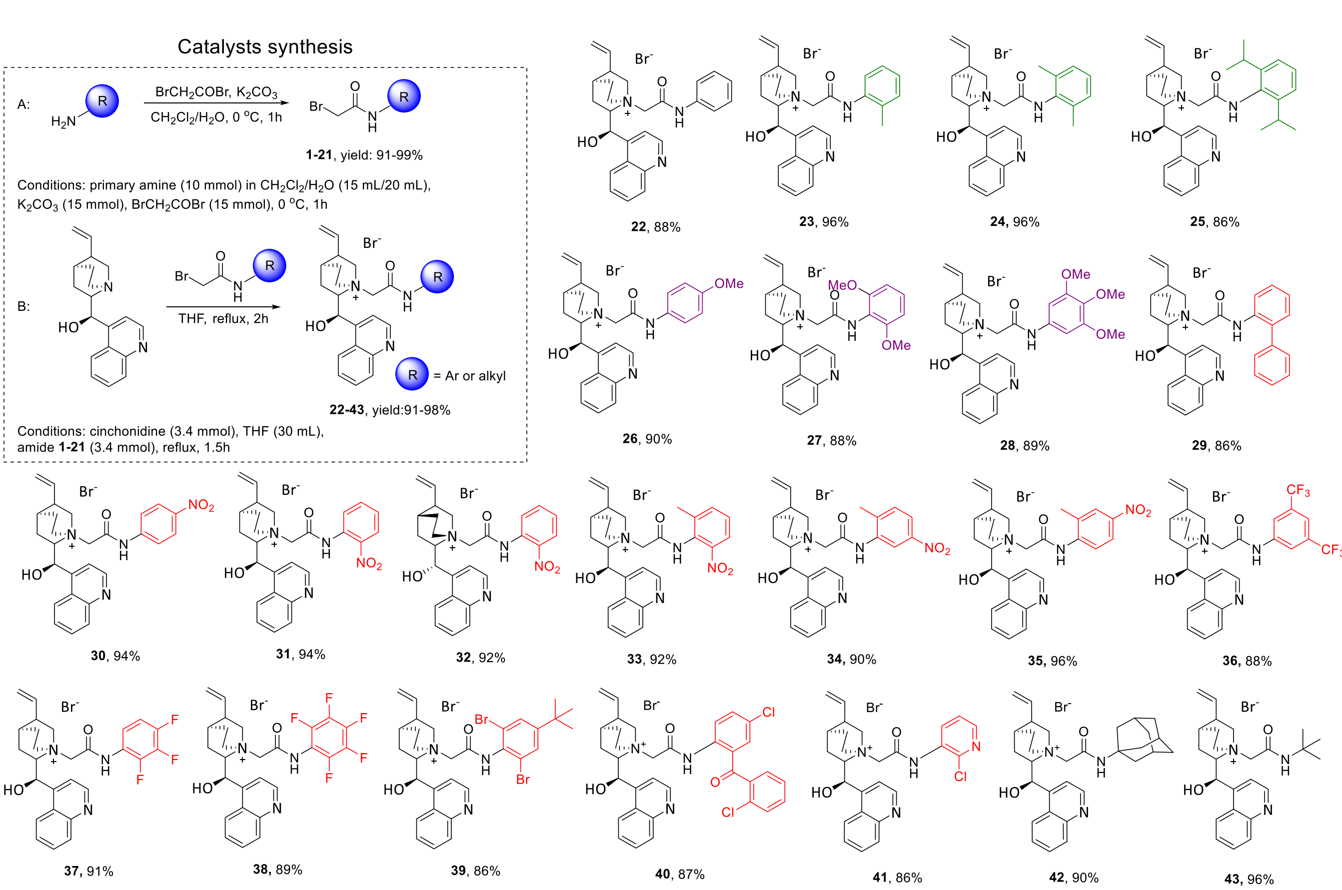
the first step (A), appropriate aniline (10 mmol) was reacted with bromoacetyl bromide (15 mmol) to obtain α-bromoamide (**1−21**), which was then used for quaternization of cinchonidine or cinchonine (step B). This reaction was carried out in boiling tetrahydrofuran (THF), giving catalysts (**22−43**) in high yield. The presented procedure for the simultaneous introduction of the amide function and the quaternary center on the nitrogen atom into the structure of the molecule does not require tedious purification processes, such as column chromatography, and pure crystalline catalyst can be easily precipitated from the reaction mixture.

With the library of catalysts **22−43** in hand, we decided to test their ability to catalyze the model reaction widely used in PTC, that is, the asymmetric benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**48**). The reaction was carried out in toluene/CH_2Cl_2 (7:3 v/v) at room temperature for 1−8 h using benzyl bromide and 50% aqueous KOH solution as a base (Scheme 3).

The screening of catalysts used in the reaction presented in Scheme 3 is presented in Figures 1 and 2, together with the yield and asymmetric induction values for product **49**. The catalysts were divided into groups based on two criteria: steric hindrance on the aromatic ring and the electronic nature (electron withdrawing group (EWG) or electron donating group (EDG)) of the substituents. For preliminary studies involving our catalysts in the alkylation reaction, we chose amide derivatives having substituents in their structure that affect the volume of steric hindrance within the aromatic ring (Figure 1a).

The increase in steric congestion in the aryl substituent of the catalyst has a positive effect on the asymmetric induction of the reaction, which is related to the inhibition of substituent R rotation. The best result, in terms of both reaction yield and enantiomeric excess, was obtained for catalyst **24** (95% yield, 67% ee). Catalysts **42** and **43** also showed very good yields but are ineffective in terms of asymmetric induction.

Scheme 2. Synthesis of Catalysts 22−43 and Overall Yields



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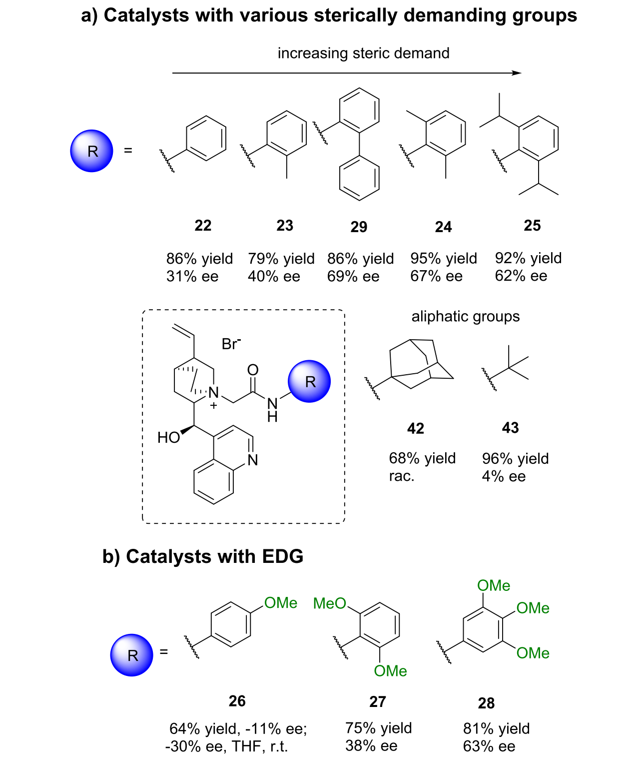

Figure 1. Catalysts with various sterically demanding groups and EDGs.

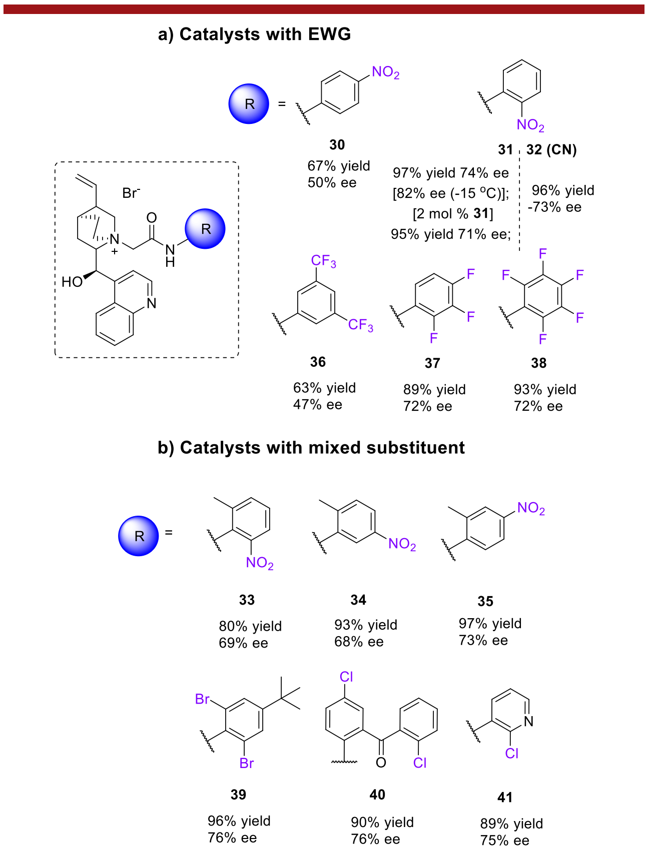

Figure 2. Catalysts with EWGs and mixed substituents.

Figure 1b shows another group of three catalysts, possessing electron-donating substituents (OMe) attached to the aromatic ring.

In this case, the asymmetric induction results strongly depended on the substitution sites of the methoxyl group in the aromatic ring of the catalyst. For the reaction involving catalyst **26**, the configuration resulting from the alkylation reaction of the product (−11% ee; −30% ee in THF) is reversed. This inverted configuration can be a reason for the weakening of the hydrogen bonds formed between the catalyst amide group and the substrate molecule as well as the adverse electrostatic interaction.

Figure 2a shows another group of catalysts, those with an electron-withdrawing substituent attached to the aromatic ring. The highest yields are demonstrated by derivatives for which it is possible to form intramolecular hydrogen bonds with the neighboring amide group, especially **31** and **32**; EWG substituents located in ortho position are responsible for this beneficial effect. In the Supporting Information, we present the crystallographic structure of one of the tested catalysts with EWG groups (**37**). The best results in the alkylation reaction were obtained for catalyst **31** (ee up to 82% at −15 °C). To check the effect of the amide group on the enantiodiscrimination of the resulting product, we also carried out an experiment using catalyst **31**, in which the amide proton was replaced with the methyl group. It turns out that replacing the amide proton in the catalyst with the methyl group decreases the ee value to 68% at −15 °C. In addition, the choice of alkaloid allows for the generation of a specific enantiomer with the complete inversion of the resulting product configuration (74% ee for **31**; −73% ee for **32**).

Finally, we tested a group of "mixed catalysts" with differing electron substituents (Figure 2b). Asymmetric induction in the alkylation reaction is similar for the catalysts shown (falling within the range of 69−76% ee) while maintaining high yields (up to 97%). In the case of nitrotoluidine regioisomers, the best result was obtained for catalyst **35** with a nitro group in the para position (97% yield, 73% ee).

In the next stage, we checked the properties of the best catalyst among those tested, namely, **31**, using different solvents in the test reaction (Figure 3). In ethereal solvents

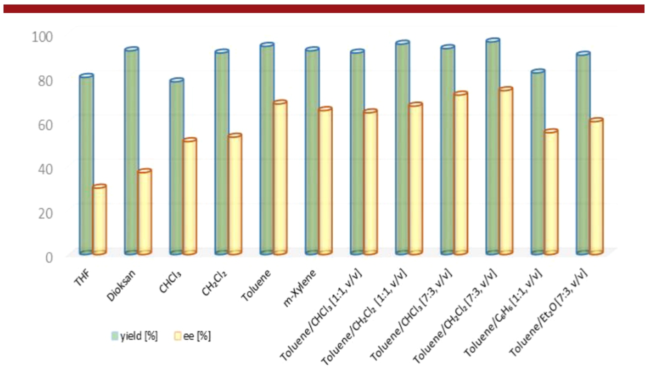

Figure 3. Screening of reaction conditions, using various solvents.

(THF and dioxane), despite very good yields, product **49** is obtained with low enantioselectivity (ee ~35%). The reaction carried out in nonpolar solvents proceeds in high yield, much better than the former one. The best results were obtained with toluene/CH_2Cl_2 (7:3 v/v) as a solvent (yield 96%, 74% ee).

According to reports in the literature,[19,20] the reduction of the double bond in the alkaloid molecule may positively affect the catalytic properties of the resulting hydroalkaloid

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derivative. Given this, we decided to synthesize four PTC catalysts (**44**−**47**) starting from cinchonidine via its dihydro derivative. The first step in the synthesis was to reduce the double bond of cinchonidine using H_2 with Pd/C as the catalyst; the product of this reaction was obtained in quantitative yield. Next, using the previously described α-bromoamides, we performed quaternization reactions under conditions analogous to those for their unsaturated counterparts to obtain catalysts **44**−**47**. The catalytic activity of compounds **44**−**47** was evaluated using the reaction shown in Scheme 3, conducted at a temperature of −15 °C for 5−8 h and with a catalyst amount reduced to 6 mol %. The reduction of the double bond had a positive effect on the catalytic efficiency of alkaloid amide derivatives in the benzylation of imine **48** (Figure 4).

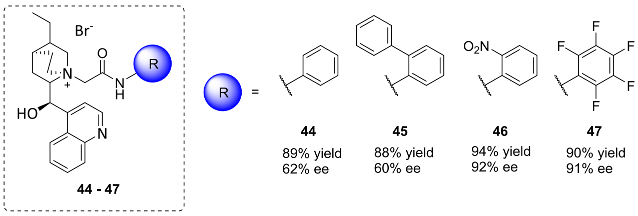

Figure 4. Hydrocinchonidine catalysts.

For catalyst **44**, a >30% increase in excess is observed with respect to its unsaturated analog **22**. The best catalyst among those obtained proved to be derivative **46**, which generates product in an excellent yield of 94% and with a very high enantioselectivity (92% ee).

In the next stage, after full screening of the catalysts used and optimization of the model reaction conditions at −15 °C, we decided to use catalyst **46** in the imine **48** alkylation with differently substituted benzyl bromides, leading to products (**49**−**55**). For comparative purposes, analogous reactions were carried out using unsaturated catalyst **31**, an analog of catalyst **46**. Reaction times ranged from 8 to 10 h.

The results in Table 1 show the effect of the substituent attached to the aromatic ring of the benzylating agent on asymmetric induction in the alkylation reaction. The best results were obtained for fluorine derivatives of benzyl bromide, especially in the ortho position (ee up to 94% for catalyst **46**). This indicates the possibility of creating additional hydrogen bonds between the catalyst and the electrophile.

In conclusion, we have successfully designed and synthesized a library of bifunctional chiral catalysts containing an amide group that demonstrate very good catalytic properties in one of the model asymmetric reactions carried out in the PTC regime. These catalysts were applied in the asymmetric alkylation of glycine derivatives with very high yields (up to 97%) and moderate to excellent enantioselectivities (up to 94% ee). The asymmetric induction strongly depends on the substituent on the phenyl ring neighboring the amide group. The best results were obtained for catalysts capable of creating internal hydrogen bonds. Further work is underway to broaden the scope of more demanding reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03065.

Synthetic procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1949618 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

Table 1. Results for Various Benzyl Bromides[a]

		catalyst 31			catalyst 46		
entry	R	time (h)	yield (%)[b]	ee (%)[c]	time (h)	yield (%)[b]	ee (%)[c]
1	H	9	94	81	8	94	92
2	2-F	8	95	90	10	97	94
3	3-F	10	92	73	9	92	86
4	4-F	8	90	81	8	94	91
5	2-Cl	8	94	83	8	92	92
6	4-Me	10	91	81	9	95	90
7	4-*t*Bu	10	90	72	10	97	83

[a]Molar ratio: RCH_2Br (5 equiv), catalyst (0.06 equiv). [b]Isolated yields. [c]ee values were determined by HPLC analysis using a chiral column Chiralcel OD-H.

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