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Aldehyde Addiction!

Organocatalytic Stereoselective Addition of Aldehydes to Acylquinolinium Ions

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Dedicated to Professor Achille Umani-Ronchi on the occasion of his 80th birthday

Abstract: A direct and simple activation of quinolines, without isolating unstable intermediates, or using isolated N,O-acetals in the presence of Lewis or Brønsted acids, is described. The procedure is quite straightforward and allows the addition in a stereoselective manner of different aldehydes to various differently substituted quinolines. The desired products were obtained in 28–76 % yields, with *dr* values up to 83:17 in favor of the *syn* isomer, and up to 99 % *ee*. Studies towards the use of acetaldehyde were also performed with different catalysts and the addition was promoted affording the desired product in 62 % yield with 46 % *ee*. Finally, deprotection and chemical transformations of the enantioenriched adducts were performed.

Introduction

The quinoline is a common motif present in several families of natural alkaloids.[1] Additionally, the related tetrahydroquinoline alkaloids[2] constitute another very important class of natural compounds that have been identified in many plants and vegetables and that often exhibit interesting biological activities (Figure 1).[3]

Enantioenriched α-substituted tetrahydroquinolines have also found important applications as synthetic intermediates and commonly used units en route to numerous pharmacologically important nitrogen-containing compounds.[4] Consequently, these molecules constitute an important class of heterocycles, as the structural motif is also found in a wide range of natural products and biologically active substances. Despite their importance, stereoselective catalytic approaches towards their preparation have found only limited success.[5] As quinolines are electron poor heterocycles, the most effective strategy for activation of the heterocyclic ring towards the attack of suitable nucleophiles involves nitrogen acylation with suitable reagents.[6] The reaction produces the corresponding acylquinolinium derivatives,[7] weak electrophiles positioned at −10/−12 of the Mayr scale,[8] that undergo reactions with various nucleophiles. Although diastereoselective addition of nucleophiles to chiral quinolinium derivatives have been reported,[9] successful early examples of activation and use of catalytic conditions were described by Shibasaki.[10] Specifically,

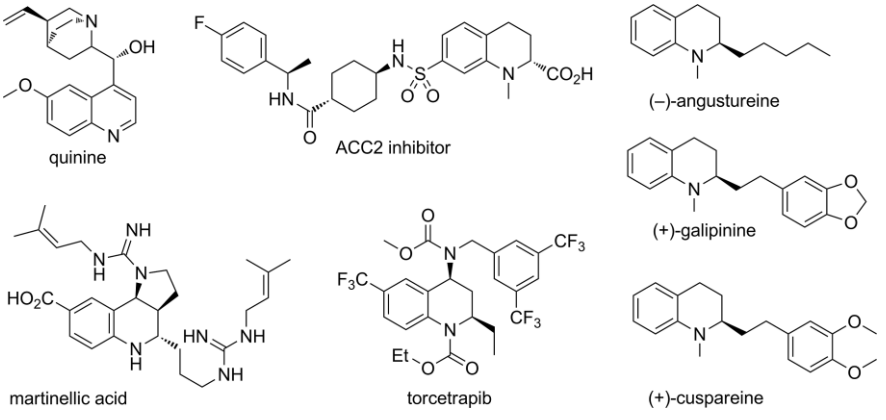

Figure 1. Natural and biologically active products containing quinoline and tetrahydroquinoline moieties.

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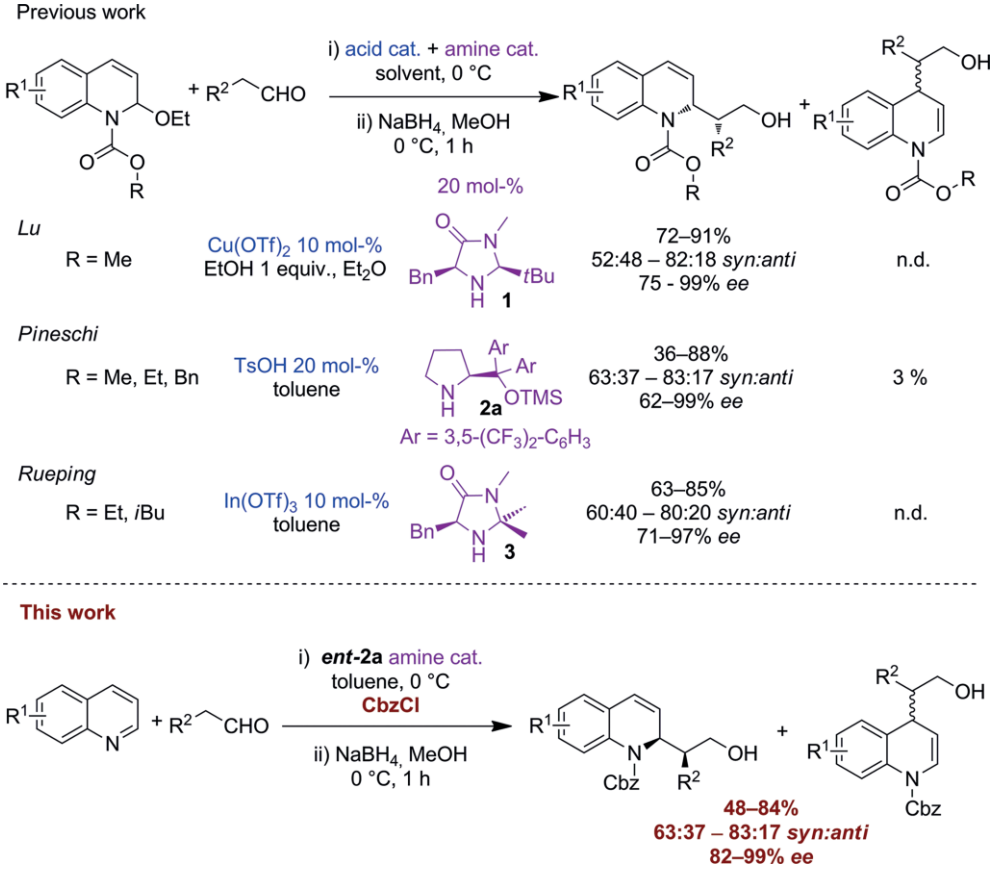
the Shibasaki work detailed the first example of a Reissert-type addition of trimethylsilyl cyanide to quinolines promoting the reaction with specifically designed bifunctional BINOL-derived ligands. Few other examples of metal-promoted addition of nucleophiles to quinolines have been reported.[11] Another quite interesting approach to enantioenriched tetrahydroquinolines employed hydrogenation promoted by metal complexes.[12] It is also worth mentioning the excellent results reported by Aponick[13] in the alkynylation of activated quinolines promoted by phosphine ligands.

With the advent of organocatalysis,[14] catalytic complementary strategies for the production of enantioenriched dihydro and tetrahydroquinolines were tested with various organocatalytic activation modes.[15] Takemoto, using non-covalent interactions, described an asymmetric Petasis[16] reaction of activated quinolines.[17] It is also worth mentioning that inexpensive tartaric acid was employed by Schaus and co-workers in the Petasis asymmetric addition of vinylboronic acids to quinolinium ions.[18] Efficient organocatalyzed asymmetric transfer hydrogenation of quinolines was described by Rueping, using an asymmetric counterion-directed catalysis (ACDC) approach.[19] Finally, Mancheño reported the alkylation of quinolinium ions with silyl enol ethers in the presence of catalysts able to surround the quinolinium as counterion.[20] All C-nucleophiles used in the addition to activated quinolines require separate preparation and thus, extra synthetic steps. On the other hand, enamine activation modes can be used to activate aldehydes and ketones towards a variety of electrophiles.[21]

Although catalytic enantioselective addition of aldehydes to carbonyls and imines was widely investigated in the past decade,[22] other electrophiles, such as alkyl halides and alkenes, were seldom used.[23] On the contrary, the stereoselective alkylation of aldehydes has been extensively investigated through the generation of stable cationic intermediates (carbenium or oxocarbenium) in S_N1-type alkylations.[24] This approach became a well-established methodology in organocatalysis.[25] In this context, the organocatalytic addition of aldehydes to *N*-acyliminiums was developed by Jørgensen, who described an enantioselective intramolecular reaction of aldehydes and isoquinoliniums. We reported an intermolecular version of the reaction,[26] and used this chemistry for a general, enantioselective and straightforward approach to 13-alkyl tetrahydroprotoberberine alkaloids.[27] It is also important to add that the generation of isoquinolinium salts by oxidation of *N*-aryltetrahydroisoquinolines and the enantioselective, oxidative cross-dehydrogenative coupling of aldehydes[28] and ketones[29] have been reported. Regarding quinolines, the S_N1 organocatalytic alkylation of quinoline N,O-acetals,[30] through generation of the acyliminium species with Lewis or Brønsted acids,[31] was recently described in the same period by three different research groups (Scheme 1).[32] However, this appealing and interesting methodology for accessing alkaloids[32b] through

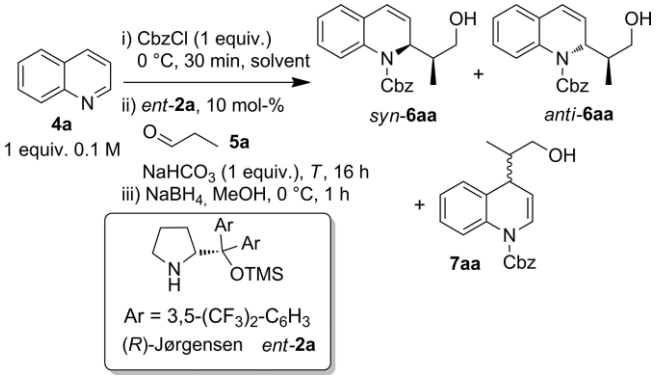


Scheme 1. Alkylation of *N,O*-quinoline acetals promoted by synergistic acid- and organo-catalysis, as well as by direct alkylation of in situ activated quinolines.

organocatalytic alkylation uses acetals, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, that need to be obtained from quinolines with an extra synthetic step. In this paper, we report our full study of the direct and simple addition of different aldehydes to various substituted commercially available or simply prepared quinolines without any extra steps leading to the reactive intermediate. In addition, we have evaluated the use of different organocatalysts and the possibility of using acetaldehyde in this chemistry. Moderate results in terms of yields and stereoselectivities were obtained.

Results and Discussion

On the basis of our previous work focused on aldehyde alkylations with isoquinolinium ions,[26] we started the current work by investigating the possible use of our established procedure in the addition of aldehydes to quinolines. Quinoline **4a** was activated by addition of CbzCl at 0 °C in anhydrous *tert*-butylmethyl ether and after 30 min, propionaldehyde **5a**, the secondary amine Jørgensen catalyst *ent*-**2a** (10 mol-%) and $NaHCO_3$ (as a base) were added to the mixture. To our delight, this simple procedure afforded the desired product in good conversion (78 %), with good enantioselectivity (86 % *ee syn*, 82 % *ee anti*) and with moderate diastereoselectivity (*syn*/*anti* = 2.8:1, see Table S1 in Supporting Information) (Scheme 2).



Scheme 2. Model reaction for the addition of propanal to quinoline, in the presence of CbzCl as an activating agent.

A control experiment performed in air and using wet *tert*-butylmethyl ether afforded no product. Quinolinium ions are sensitive electrophiles and an excess of water decomposes the activated quinoline species. As was stated in the introduction, three reports by Lu, Pineschi and Rueping have described the asymmetric alkylation of quinoline N,O-acetals with aldehydes using catalysts **1**, **2a**, and **3** via a synergistic enamine-acid catalysis system in the presence of Lewis[32a,32c] or Brønsted acids.[32b] In all cases, products were obtained by using the preformed N,O-acetals, generated by the reaction of quinoline derivatives with acylating agents in the presence of ethanol. As in the employment of N,O-acetals, activation by Lewis or Brønsted acids is mandatory, different organocatalysts can suffer from decomposition. In fact, when a Lewis acid was used, the MacMillan imidazolidinone-based catalysts enabled improved yields. In addition, it has been reported that the Jørgensen catalyst can be quickly desilylated in unfavorable reaction conditions.[33]

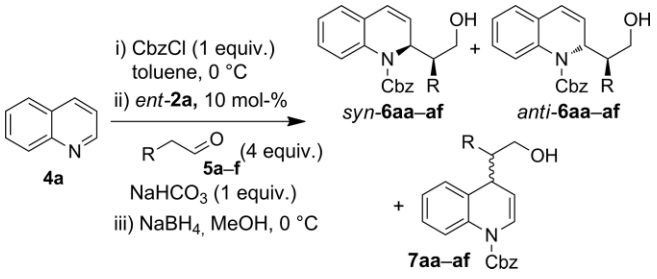
The alkylation of aldehydes with quinolines activated in situ using benzyl chloroformate was optimized by screening different solvents and temperatures using four equiv. of propionaldehyde and 10 mol-% of the Jørgensen catalyst. The optimal solvent was toluene, whereas the application of other solvents (see Table S1 in Supporting Information for further details) rendered inferior results. The methodology described here is substantially different from previous reports because there is no need to presynthesize quinoline N,O-acetals and, thus, there is no need for a Brønsted or Lewis acid co-catalyst. GC–MS was used to evaluate the crude reaction mixtures after 16 h. The reaction products were isolated as the corresponding alcohols, after reduction with a slight excess of $NaBH_4$ and dilution with MeOH. Diastereomeric ratios and enantiomeric excesses were determined by chiral HPLC on the crude alcohols. Although the 2 position of the quinoline represents the activated electrophilic carbon, small amounts of 4-substituted products **7** (6–18 %) were always observed. These byproducts were always separated from the desired major *syn* product after chromatographic purification. Increasing the amount of base led to a slight reduction in conversion although, in its absence, reactions proceeded to a much lower extent. One equiv. of acylating agent allowed the efficient activation of quinoline avoiding the catalyst deactivation. It is also worth noting that, contrary to the case with isoquinolines, the slow addition of activating agent by syringe pump is not mandatory in this case.[24] Other acylating agents were tested instead of benzyl chloroformate; the use of ethyl chloroformate afforded similar results in terms of stereoselectivity but led to reduced product yields (product **10** see Supporting Information). The use of TrocCl as a potential activating agent failed to afford product.

Although products containing an aldehydic group are less stable, they can be isolated by quenching the reaction with MeOH (to consume unreacted CbzCl), and subsequent evaporation of reaction solvent under reduced pressure, followed by direct purification by silica gel column chromatography. In the case of propanal, the aldehydic product was indeed isolated with slightly reduced yields (about 70 %) compared to the reductive work-up. However, it was not possible to obtain analytically pure product by chromatographic purification, as it was contaminated with the secondary amine catalyst. Moreover the major *syn* diastereoisomer could not be separated from the minor *anti* isomer or from the product obtained by alkylation in C-4 position. In light of such limitations, along with the recognized higher stabilities offered by alcohol products, we chose to isolate all products following a reductive work-up.

With the optimized conditions in hand we then explored the scope of the methodology using different aldehyde and quinoline reaction partners (Table 1).

Enantioselectivities were optimal for linear aliphatic aldehydes and hydrocinnamaldehyde, whereas when the α position of the aldehyde incorporated a bulky group, such as phenyl or isopropyl, *ee* values decreased to approximately 80 %. The diastereoselectivities observed with the variety of aldehydes in-

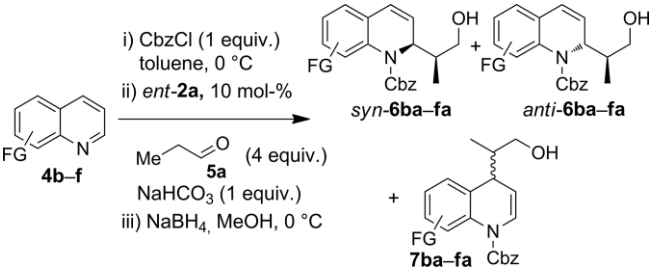
Table 1. Scope of the functionalization of quinolines with different aldehydes promoted by the Jørgensen catalyst.



Entry[a]	R	Prod.	*syn/anti*:**7**[b]	*ee syn*[c] [%]	*ee anti*[c] [%]	Yield *syn*[d] [%]
1	Me	**6aa**	63:21:16	94	93	53
2	*n*-C_6H_{13}	**6ab**	70:16:14	93	95	58
3	Ph	**6ac**	58:26:16	82	34	54
4	$PhCH_2$	**6ad**	54:23:23	99	96	43
5	$(CH_3)_2CH$	**6ae**	63:37:0	81	77	39
6	H	**6af**	100[e]:0	4	–[e]	76[e]

[a] All reactions were carried using 0.2 mmol of quinoline, CbzCl and $NaHCO_3$, 0.8 mmol of aldehyde and 0.02 mmol of the cat. *ent*-**2a** for 16 h at 0 °C. [b] Determined by ^{1}H-NMR on the crude reaction mixture; **7** is present as a mixture of diastereoisomers. [c] Enantiomeric excesses were measured by chiral HPLC after chromatographic purifications. [d] Yield of isolated *syn*-**6aa**–**af** after chromatographic purification. [e] For **6af** no diastereoisomers were formed.

Table 2. Addition of propanal to various substituted quinolines.



Entry[a]	FG	Prod.	*syn/anti*:**7**[b]	*ee syn*[c] [%]	*ee anti*[c] [%]	Yield *syn*[d] [%]
1	6-Br	**6ba**	61:28:11	94	92	28
2	6-OMe	**6ca**	74:15:11	96	90	57
3	5-Br	**6da**	46:39:15	91	89	44[e]
4	6-allyl	**6ea**	64:20:16	90	91	49
5	6-Ph	**6fa**	50:32:18	92	82	41[f]

[a] All reactions were carried out using 0.2 mmol of quinoline, CbzCl and $NaHCO_3$, 0.8 mmol of aldehyde and 0.02 mmol of the cat. *ent*-**2a** for 16 h at 0 °C. [b] Determined by ^{1}H-NMR on the crude reaction mixture; **7** is present as a mixture of diastereoisomers. [c] Enantiomeric excesses were measured by chiral HPLC analysis after chromatographic purification. [d] Yield of isolated *syn*-**6ba**–**fa** after chromatographic purification. [e] Inseparable mixture of *syn*-**6da**/*anti*-**6da**/**7da**. [f] Inseparable mixture of *syn*-**6fa**/**7fa**.

vestigated proved to be only moderate. Acetaldehyde gave similar results in terms of yield (76 %). However, and more importantly, the reaction with acetaldehyde afforded almost no enantioselectivity (4 % *ee*); this is likely a reflection of the moderate to low diastereoselectivity combined with the absence of an α-substituent leading to a lack of facial selectivity for the putative enamine intermediate.

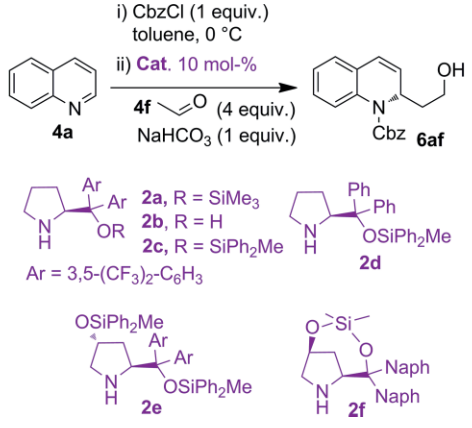
Quinoline substitution patterns strongly influence reaction outcomes using the detailed reaction conditions. Substituents at positions 5 and 6 of the quinoline ring were well tolerated, and in these cases (Table 2, Entries 1–5) we were able to obtain the desired products with good *ee* values and moderate diastereoselectivities. The isolated yields were satisfactory when neutral or electron-donating groups were present on the quinoline ring. However, when bromine was inserted, a decrease in reaction yield was observed. The presence of strong electron-withdrawing groups, such as the nitro group on the isoquinoline ring, strongly inhibited the reaction. Steric hindrance considerations imposed by quinoline substituents were also found to influence reactivity. In fact, the presence of a methyl group at the 8 position dramatically inhibits the reaction, according to previous reports;[20] this is likely the result of impaired acylation needed to form the corresponding quinolinium ion.

The use of 4-hydroxyquinoline failed to give rise to any desired product. Instead, the hydroxyl group reacted with the acylating agent under the reaction conditions. 4-Methoxyquinoline, obtained by alkylation of the 4-hydroxyl moiety, was found to be less soluble in toluene. However, even the addition of co-solvents such as CH_2Cl_2 and employing a mixture of CH_2Cl_2/toluene (1:1), failed to afford the desired product. Notably, 4-methoxyquinoline can behave as an activated nucleophile and this may explain the failure of this reaction. Finally, we evaluated the reactivity of 2-methylquinoline to see if increasing steric hindrance at position 2 might aid in directing aldehyde attachment to the quinolone C-4. However, this effort also failed to afford any desired adduct. For all the quinolines or aldehydes tested [except for isovaleraldehyde (Table 2, Entry 5)], small amounts of the C-4 addition products were observed (5–16 % yield). In most cases, these undesired products could be efficiently eliminated by flash column chromatography or by preparative TLC on silica after reduction to the corresponding alcohols. In some cases, the *anti* product was obtained as a component of a mixture containing undesired products **7**. However, major *syn* diastereoisomers could always be separated from the minor *anti* diastereoisomers, (with the exception of **6da**), and isolated as pure compounds. In the cases of **6ac** and **6ad**, the minor products could not be separated from the alcohols derived from reduction of excess of aldehyde starting materials. Notably, products **6** are very stable compounds that can be conserved at –20 °C in sealed vials under air for 1 year without any degradation. Conversely, products **7** are quite unstable. For instance, isolated **7ab** decomposed in a matter of just a few weeks.

The reaction between acetaldehyde and quinoline affords corresponding product **6af** in good yield, but with low stereoselection. Because this adduct can be a valuable starting material for the synthesis of the Galipea alkaloids,[3] we decided to investigate more deeply this transformation using different catalysts and conditions. It is also worth mentioning that the strategies published with N,O-acetal quinoline derivatives proceed in a maximum 25 % *ee* with respect to acetaldehyde addition.[32] Catalysts **2c**–**f**[34] were prepared using straightforward reactions.[35] All the catalysts were investigated in different sol-

vents, and the salient results obtained are reported in Table 3. Interestingly, commercially available catalyst **2b**[36] was found to be active (37–39 % *ee*), although low yields of desired product were noted when the reaction was carried out in CH_3CN or DMF; no reaction was observed when using toluene as solvent. The use of a bulkier silyl substituent (catalyst **2c**) led to an added increase to 46 % *ee* while at the same time enabling a good yield. The use of catalyst **2d**, bearing phenyl groups instead of the bis-trifluoromethylated aryl moieties, led to a slight decrease in *ee*. To achieve a better result we sought to impose a higher degree of control over the electrophile's approach to the enamine.

Table 3. Various organocatalysts employed to promote the addition of acetaldehyde to quinoline, in the presence of CbzCl.



Entry[a]	Cat.	Solvent	*ee* [%][b]	Conversion[c]	Yield [%][c]
1	*ent*-**2a**	toluene	4 (*R*)	89	76
1	**2b**	toluene	–	–	
2	**2b**	DMF	37 (*S*)	19	
3	**2b**	CH_3CN	39 (*S*)	23	
4	**2c**	toluene	46 (*S*)	74	62
5	**2d**	toluene	40 (*S*)	32	
6	**2e**	toluene	10 (*R*)	48	
7	**2f**	toluene	22 (*S*)	56	

[a] All reactions were carried on 0.2 mmol of quinoline, CbzCl and $NaHCO_3$, 0.8 mmol of acetaldehyde and 0.02 mmol of the cat. *ent*-**2a**, **2b**–**f** for 16 h at 0 °C. [b] Enantiomeric excesses were measured by chiral HPLC analysis of the crude reaction mixture, after reduction. [c] Conversions were determined by GC–MS analysis before reduction. [d] Yield of isolated products after chromatographic purification.

We hypothesized that the presence of a bulkier group on the less hindered face of the catalyst, would reduce the number of possible approaches for the electrophile in the reaction with the enamine thereby increasing enantioselectivity. With this in mind, novel catalyst **2e**, derived from *trans*-4-hydroxyproline, was prepared (see Supporting Information for synthetic details). The *trans* substituent had a strong, but detrimental, effect on the reaction outcome and the product was obtained with only 10 % *ee*. In addition, the use of (*S*)-**2e** having the bulky *trans*-oriented substituent at the 4 position of the pyrrolidine ring, led to the enantiomeric product, compared to the products obtained with all other investigated (*S*)-prolinol catalysts. Notably, previously described constrained catalyst **2f**[37] was found to be unsuitable for the desired transformation.

It is likely that the presence of enhanced steric hindrance attributable to the *trans* substituent influences the face of the quinolinium ion that approaches the enamine. However, solvents and entropic effects[38] cannot be neglected considering that the enantiomeric excess of isolated product was quite low.

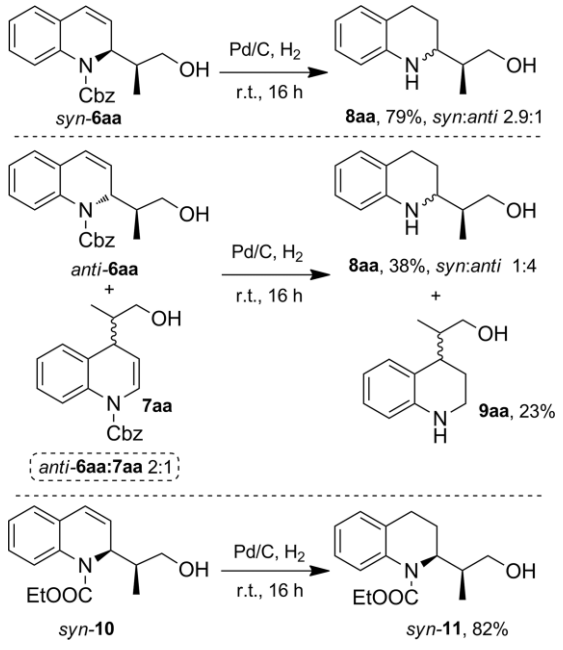
Recently Pihko[39] reported the use of a 5-*trans*-aryl-substituted prolinol catalyst in Mukayama–Michael reactions. These effective new catalysts gave better results by exploiting secondary interactions, and we are planning to investigate further similar interesting opportunities with additional work.

The relative and absolute configurations of the obtained products were assigned by comparing the ^{1}H-NMR traces and the specific rotations with the corresponding products already reported in the literature.[32b] The reported characteristic ^{1}H-NMR signals of *syn*-**6aa** and *anti*-**6aa** were compared with our products and the *syn*-relative configuration was easily assigned to the major product and the *anti*-relative configuration to the minor product. The assigned relative configurations were further confirmed by comparing the elution orders of **6aa** with those reported by Pineschi (see Supporting Information for details). The absolute configuration of product **6ac** was determined by isolating the pure *syn* diastereoisomer and comparing its specific rotation with the one previously reported in the literature.[32b,40] The (*S*,*S*) absolute configuration was then assigned by analogy to all *syn*-**6aa**–**fa** products.

Having verified the scope and limitations of the methodology, we investigated possible derivatizations of model substrate **6aa**. Standard hydrogenation conditions were tested in order to remove the Cbz group and reduce the 3,4-double bond. When *syn*-**6aa** was dissolved in methanol and reacted under an atmosphere of H_2 in the presence of 10 % wt Pd/C, tetrahydroquinoline product **8aa** was obtained in good yield, but as a 2.9:1 mixture of *syn*/*anti* diastereoisomers (Scheme 3).

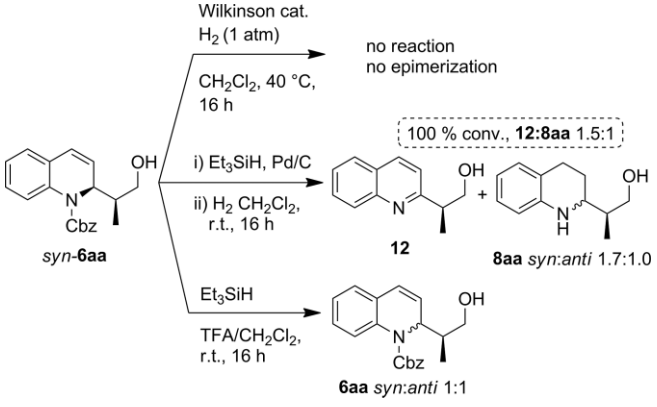
The relative configuration of the tetrahydroquinoline diastereoisomers, was confirmed by subjecting the *anti* diastereoisomer to the same hydrogenation conditions. In this case, a less significant epimerization was observed and product **8aa** was obtained with a reversed diastereomeric ratio *syn*/*anti* of 1:4. From these reactions it was evident that cleavage of the Cbz group leads to partial epimerization of both *syn*-**6aa** and *anti*-**6aa**; in the case of *syn*-**6aa** this appears to happen to greater extent than is the case for other substrates. As the final diastereoisomeric ratio is different starting from *syn*-**6aa** or *anti*-**6aa**, it is reasonable to assume that the deprotection-hydrogenation reaction occurs faster than the epimerization process which cannot reach its thermodynamic equilibrium. It is important to note that when we subjected to the same hydrogenation conditions, products *syn*-**10** and *anti*-**10**, having the ethyl carbamate instead of Cbz, no epimerization was observed. Moreover, the corresponding products of these reactions were obtained as single diastereoisomers, in agreement with earlier Rueping findings (see Supporting Information).[32c]

Several other conditions were tested, but we were unable to avoid partial epimerization. In addition, whereas the Wilkinson catalyst left the starting material completely untouched, other conditions reported by Mancheño,[20] for hydrogenation of *N*-Troc dihydroquinolines, gave a 1.5:1 mixture of re-aromatized



Scheme 3. Hydrogenation conditions for cleavage of Cbz and COOEt groups from *N*-protected substrates.

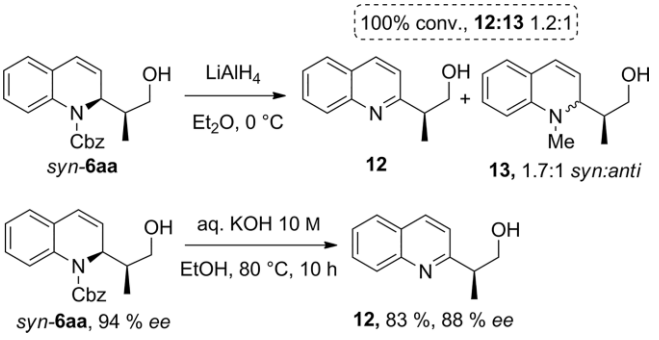
quinoline **12** and desired deprotected product **8aa** as a mixture of diastereoisomers (Scheme 4).



Scheme 4. Different reductive conditions for deprotection and full hydrogenation of the isolated enantioenriched adducts.

Finally, selective reduction of the double bond, leaving the Cbz group in place, as we have demonstrated in the case of isoquinoline adducts,[26] was tested. Isolated *syn*-**6aa** was treated with Et_3SiH in TFA/DCM at room temperature, but no conversion was observed. Instead, the recovered starting material was a 1:1 *syn*/*anti* mixture. The epimerization likely proceeds through a shift of the double bond and re-protonation under the acidic conditions.

Treatment of *syn*-**6aa** with $LiAlH_4$ at 0 °C with the intention of converting the Cbz group to the corresponding methyl group, a structural motif recurring in most of the tetrahydroquinoline alkaloids, unfortunately afforded a complex mixture of products. The major characterized product was consistent with loss of the Cbz group and re-aromatization of the quinoline ring, whereas desired product **13** was present as mixture of diastereoisomers (Scheme 5).



Scheme 5. Re-aromatization of *syn*-**6aa** with reductive and hydrolytic conditions.

Re-aromatization can be envisioned to involve $LiAlH_4$-mediated deprotonation of the 2-allylic proton followed by loss of the Cbz group or by hydrolysis of the benzyl carbamate by adventitious water followed by decaboxylation of the resulting quinoline-1(2*H*)-carboxylic acid. In fact, when **6aa** was treated in EtOH with concentrated solution of KOH, according to Rueping report,[32c] the re-aromatized product was isolated in 83 % yield and in 88 % *ee*. This strategy enables ready access to enantioenriched quinolines bearing a chiral substituent at the 2 position. Although deprotection and reduction chemistries are possible with these adducts, successive purifications are necessary to separate the resultant diastereoisomeric mixtures.

Conclusions

In conclusion, we have reported the first direct organocatalytic enantioselective alkylation of aldehydes with quinolines activated with benzyl chloroformate. The reaction uses a commercially available prolinol catalyst, and proceeds without the aid of an acidic co-catalyst. The reaction gives good results with all the tested aldehydes and with 5- or 6-substituted quinolines, affording the desired 2-alkylated products in moderate to good yields. The reaction also proceeds with good regioselectivity; 4-alkylation products are present in minor amounts relative to the desired C-2 addiction products. The synthesis of modified Jørgensen catalysts allowed us to obtain a 46 % *ee* for the alkylation of acetaldehyde with quinoline; thus far, this constitutes the optimal result for this coupling.

The products generated in this fashion can be efficiently re-aromatized to the corresponding 2-alkylquinolines having a stereocenter at the position adjacent to the aromatic ring. Detailed investigations into deprotection and hydrogenation of the *N*-Cbz products en route to 2-alkyl tetrahydroquinoline products revealed an unexpected epimerization process. Efforts to apply this methodology to the synthesis of alkaloids and natural products will be the subject of future studies in our laboratory.

Experimental Section

General Procedure for the Alkylation of Aldehydes with Quinolines: In a flame-dried two-necked round-bottomed flask

equipped with a magnetic stirring bar under nitrogen atmosphere, quinoline **4a**–**f** (0.2 mmol) was dissolved in anhydrous toluene (2 mL) at 0 °C. Then CbzCl (0.2 mmol, 31 μL) was added and the solution rapidly turned into a white suspension. After 30 min, $NaHCO_3$ (0.2 mmol, 17 mg), Jørgensen catalyst *ent*-**2a** (0.02 mmol, 12 mg) and aldehyde **5a**–**f** (0.8 mmol) were added and the mixture was stirred for 16 h at 0 °C. Methanol (0.5 mL) and $NaBH_4$ (1.6 mmol, 61 mg) were then added, and after complete conversion as judged by TLC analysis (1–2 h), the reaction was quenched by addition of aq. HCl 1 M until pH = 2 at 0 °C. EtOAc (5 mL) was then added and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 8 mL). The collected organic layers were washed with brine (10 mL), dried with Na_2SO_4 and concentrated under reduced pressure to give the crude products. Chromatographic purification ultimately afforded desired product **6**.

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Keywords: Organocatalysis · Enantioselectivity · Aldehydes · Alkaloids

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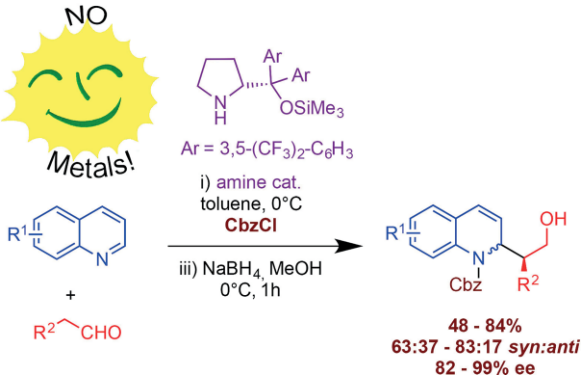

A variety of aldehydes are added in a straightforward and organocatalytic manner to activated quinolines. The procedure is simple, employs commercially available organocatalyst, does not require an additional step for quinoline activation, and requires no Lewis acidic metals. The reaction is characterized by good yields, moderate diastereoselectivity, and excellent *ee* values.

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