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A Bifunctional β-Isocupreidine Derivative as Catalyst for the Enantioselective Morita–Baylis–Hillman Reaction and a Mechanistic Rationale for Enantioselectivity

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Dedicated to Professor Gianni Porzi on the occasion of his retirement

Keywords: Asymmetric catalysis / Computational chemistry / Donor-acceptor systems / Enantioselectivity / Transition states

Starting from β-isocupreidine (β-ICD), a series of difunctional catalysts were synthesized to ascertain their usefulness in the asymmetric Morita–Baylis–Hillman (MBH) reaction. The trichloroacetylcarbamate derivative was found to give the (*R*)-MBH adducts in excellent optical purities (90–99 % *ee*) and moderate to good yields (43–83 %), in some cases, better than β-ICD. A number of acrylates were also tested and 2,6-dimethyl-4-nitrophenyl acrylate was identified as a suitable alternative to the popular hexafluoroisopropyl acrylate, with both the β-ICD and trichloroacetylcarbamate derivatives. The mechanism of the rate- and selectivity-determining step was ascertained by means of experimental observations and a computational investigation aimed at clarifying the transition state structures is reported. These studies have clarified the reasons for the effectiveness of these structurally related catalysts in the asymmetric MBH reaction between acrylates and aldehydes.

Introduction

The Morita–Baylis–Hillman (MBH) reaction is a very appealing transformation for synthetic purposes because the α-methylene-β-hydroxycarbonyl products are highly valuable intermediates in organic synthesis.[1,2] However, despite great efforts directed towards the optimization of asymmetric methodologies,[1,3] until now only partial success has been obtained; the reaction between acrylates and common aldehydes has been particularly challenging.[4]

In fact, the most efficient approach to highly enantioenriched 2-methylene-3-hydroxycarbonyl alkanoates is still represented by the β-isocupreidine (β-ICD)/hexafluoroisopropyl acrylate (HFIPA) method,[5] the yields and applicability of which has recently been slightly improved through the use of azeotropically dried β-ICD,[5d] and extended in scope with the introduction of an enantiocomplementary catalyst derived from quinine.[5c] However, reactions using these methodologies must be performed at low temperature (–55 °C), sometimes for prolonged periods, and the yields are somewhat erratic. Moreover, when the reactive *p*-nitrobenzaldehyde or aliphatic aldehydes are used, the high *ee* value of the products is partially due to a kinetic resolution that removes most of the minor enantiomer by formation of substantial amounts of undesired dioxanones.[6]

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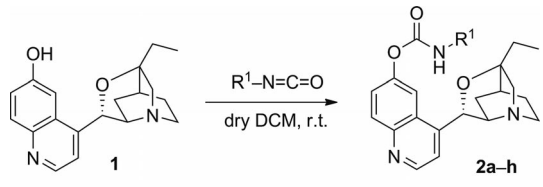
Results and Discussion

Methodology Development and Optimization

Taking advantage of our previous experience within the extension of hydroxy functionalities by means of electrophilic reagents,[7] we devised a method to convert the free phenolic hydroxy group of β-ICD (**1**) into a carbamate or an acyl carbamate (Scheme 1).



a: R^1 = $CCl_3C{=}O$ **e**: R^1 = $C_6H_5CH_2$
b: R^1 = *p*-$O_2NC_6H_4C{=}O$ **f**: R^1 = (*R*)-$C_6H_5(CH_3)CH$
c: R^1 = $C_6H_5C{=}O$ **g**: R^1 = (*S*)-$C_6H_5(CH_3)CH$
d: R^1 = $CH_3C{=}O$ **h**: R^1 = $C_6H_5(C{=}O)NHCH_2CH_2$

Scheme 1. Synthesis of catalysts **2a**–**h**.

According to this strategy, derivatives **2a**–**h** were obtained in moderate to good yield by reaction of the phenolic

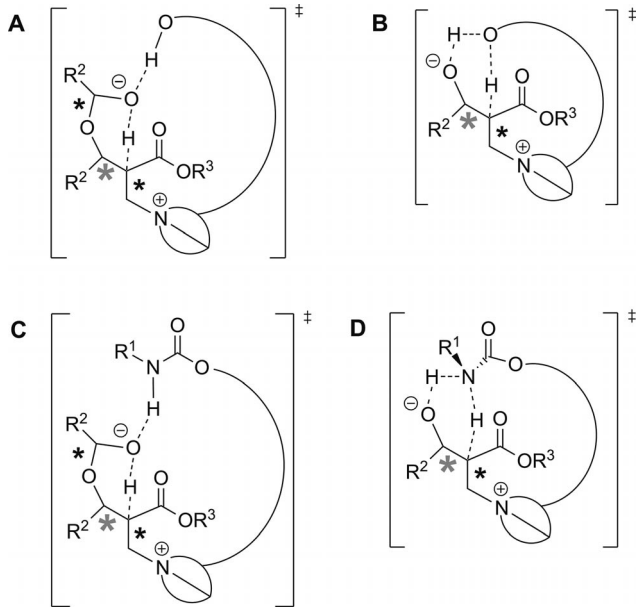
functionality of **1** with a series of isocyanates and acyl isocyanates, which were prepared according to literature methods.[8] It was readily apparent that for catalysts **2a**–**h** the acidity of the NH proton of the resulting carbamates, or acyl carbamates, can be easily modulated by appropriately choosing the R^1 group. Thus, both the positioning of this acidic functionality, which is clearly different from that of the parent hydroxyl group, and the variety of R^1 groups, lead to very different steric requirements in all the reaction steps in which they participate. In particular, it has recently been determined both experimentally and computationally that the rate-determining (and product-determining) step in the MBH reaction is not the formation of the C–C bond during the aldol reaction between the zwitterionic enolate and the aldehyde, which is essentially a rapid equilibrium, but rather the proton transfer in the adduct that causes the successive regeneration of the catalyst.[9]

However, it has also been stated that for reactive aldehydes, in which the addition step is more exothermic, there could be a reduced reversibility and consequently a concurrence, at least partial, of the stereoselectivity of the addition step to the overall result.[9f] A similar behaviour could be the basis of the higher selectivities generally obtained in the *aza* counterpart of the MBH reaction (*aza*-MBH), in which the addition to N-activated imines is more exothermic than addition to aldehydes. Thus, in these cases, an enhanced selectivity due to the clearer discrimination between the four possible diastereomers of the aldol addition step, with respect to that between the four or eight diastereomers (vide infra) present in the proton transfer step, cannot definitely be excluded.

The large amount of data available from kinetic experiments, ESI-MS identification of elusive key intermediates, and computational studies indicate that, depending on the specific reaction conditions, there will be a prevalence of one of the two competing mechanisms for the proton transfer, namely pathways proposed by McQuade[9b,9c] and Aggarwal.[9e,9f] Referring to our particular system and focusing on the aspect of stereoselection, based on both the proposed mechanistic possibilities in the rate-determining proton transfer step, the following observations can be made about the effects that could be brought about by structural and electronic changes passing from **1** to **2a**–**h** (Scheme 2).

In particular, the proton transfer step should occur predominantly through a six-membered transition state − McQuade pathways, **A** for β-ICD (**1**), and **C** for catalysts **2a**–**h** − at the early stage of the reaction and in absence of protic species, after the formation of a hemiacetal species by addition of a second molecule of aldehyde.

Thus, supposing a rapid and complete equilibration of all the eight possible diastereomers with their respective conformers, the success in obtaining high *ee* values closely relies on the ability of the hydrogen-bond donor functionality to selectively promote the proton transfer from one (or more) of the diastereomers possessing the desired absolute configuration of the carbon indicated in Scheme 2 with the asterisk printed in grey.



Scheme 2. Transition states **A**–**D** and the possible roles of catalysts **1** and **2a**–**h** on the rate-determining and selectivity-determining step (proton transfer).

In the presence of protic sources (i.e., the acidic functionality of the catalyst) or by intervention of the MBH adduct itself in the late stage of the reaction, another six-membered transition state could be formed; Aggarwal pathways, **B** for β-ICD (**1**), and **D** for catalysts **2a**–**h**. Hypothesizing again a thermodynamic equilibrium of all the steps preceding the proton transfer, the selectivity of the reaction will rely on the ability of the acidic moiety to act predominantly as a proton shuttle, by means of six-membered transition states, on only one of the four possible diastereomers or, alternatively, to the two diastereomers displaying the same configuration at the carbon indicated by the asterisk printed in grey in Scheme 2.

Within this scenario, the possible effects of changing the acidic functions in the series **2a**–**h** with respect to β-isocupreidine (**1**), can be examined. The ability of the various NH groups to favour the reaction from a particular diastereomer will be different to that of the OH group in **1**, due to the clear geometrical distortions that come about because of the change in the distance from the phenolic oxygen, leading to a different positioning of the negatively charged oxygen.

In addition, the R^1 substituent will also have a strong effect on the acidity of the NH group, changing the charge transfer interaction with the negatively charged oxygen. Consequently, the actual basicity of the hemiacetalic oxygen should be inversely dependent on the amount of negative charge transferred to the NH hydrogen. Because a less reactive system should allow better discrimination between the various diastereomers, a better selectivity would be expected for catalysts with a more acidic NH function.

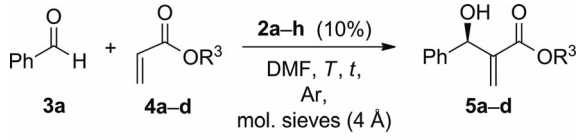
The alkyl or acyl substituents R^1 in catalysts **2a**–**h** differ greatly both in steric bulk and in the hybridization at the carbon atom attached to the nitrogen. The proton transfer

should be favoured for cases in which there is less destabilizing interaction with the rest of the molecule, in particular with the R^2 groups.

Having compounds **2a**–**h** in hand, all displaying the extended functionality, we undertook a screening to ascertain their usefulness as catalysts for the enantioselective MBH reaction. With the aim of evaluating whether these catalysts may be good candidates with respect to realistic reaction times, we chose to use a relatively poorly reacting aldehyde, benzaldehyde, during the optimization.

For the acrylate partner in the reaction, we decided to use relatively activated species that possess differing steric bulk and preferred conformations, such as α-naphthyl acrylate (**4b**), which has already been used in enantioselective MBH reactions,[3a,3b,10] 4-nitrobenzyl acrylate (**4c**), and two 2,6-dimethylphenyl derivatives having a methyl (**4a**) or a nitro (**4d**) group at position 4 of the aromatic ring (Table 1), respectively. The acrylates were freshly prepared and used free of impurities (including stabilizer), to avoid possible mechanistic interference.

Table 1. Synthesis of adducts **5a**–**d** catalyzed by **2a**–**h**.



3a 4a–d 5a–d

a: R^3 = 2,4,6-$(CH_3)_3$-C_6H_2 **c**: R^3 = 4-NO_2-C_6H_4-CH_2
b: R^3 = 1-naphthyl **d**: R^3 = 2,6-$(CH_3)_2$-4-NO_2-C_6H_2

Entry[a]	4	Cat	*T* [°C]	*t*	Yield, %[b] (*ee*, %)[c]
1	**4a**	**2a**	–18	20 d	71 (85)
2	**4a**	**2b**	–18	10 d	7 (75)
3	**4b**	**2a**	–18	18 d	43 (70)
4	**4c**	**2a**	–18	23 d	78 (45)
5	**4d**	**2a**	0	18 h	38 (89)
6	**4d**	**2c**	–18	2 d	–[d]
7	**4d**	**2d**	–18	3 d	21[e] (79)
8	**4d**	**2f**[f]	0	24 h	16 (78)
9	**4d**	**2g**[f]	0	24 h	15 (76)
10	**4d**	**2h**[f]	r.t.	5 d	55 (58)

[a] Reagents and conditions (1 mmol scale): aldehyde, acrylate (1 equiv.), catalyst (10 mol-%), anhydrous DMF (0.3 mL). [b] Yield of pure isolated product. [c] Determined by HPLC analysis. [d] Only dimerization of acrylate was observed. [e] Product not separated from byproducts. [f] Partial decomposition of catalyst was observed.

Initially, a brief survey of various solvents and amounts of catalyst demonstrated that, as for β-ICD, anhydrous *N*,*N*-dimethylformamide (DMF) was needed together with at least 10 mol-% catalyst to achieve the best results in terms of both enantioselection and reaction rate. Thus, catalysts **2a**–**h** and acrylates **4a**–**d** were tested with benzaldehyde under these conditions at various temperatures (Table 1). Compound **2e** decomposed to a great extent during chromatographic purification.

Acrylate **4a** underwent very clean reactions, however, it was very slow to react (Table 1, entries 1 and 2). In particular, with catalyst **2b** (R^1 = 4-nitrobenzoyl, Table 1, entry 2) only 7% yield was obtained after 10 days reaction at –18 °C, strongly suggesting that, in this case, the activity of the catalyst was greatly reduced by the high acidity of the NH hydrogen. However, we were pleased to observe that by using catalyst **2a** (R^1 = trichloroacetyl, Table 1, entry 1), product **5a** was obtained in good yield and with an encouraging 85% *ee*. Moreover, the product could be easily recrystallized to give 98% *ee* with a final yield of 55%.

Catalyst **2a** was then used in conjunction with acrylates **4b**–**d** (Table 1, entries 3–5), leading to a very rapid and selective reaction with 2,6-dimethyl-4-nitrophenyl acrylate (DMNPA) **4d** (Table 1, entry 5), albeit in low yield. However, we observed that most conversion occurred very rapidly in the initial phase of the reaction, and was then significantly slowed by the formation of substantial amounts of the dioxanone derivative with concomitant production of 2,6-dimethyl-4-nitrophenol. This latter product is sufficiently acidic to greatly suppress the catalytic activity by acid-base reaction with the basic nitrogen of **2a** (pK_a of the parent 4-nitrophenol is 7.14 in H_2O, whereas quinidine, which is probably less basic than **1** and **2a**, has a pK_a of conjugate acid of 7.95 and quinuclidine has a pK_a of conjugate acid of 11.0[11]).

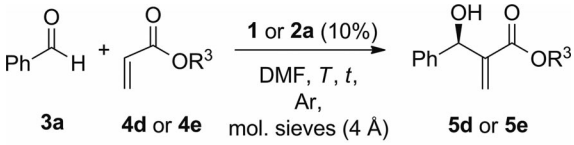
Taking DMNPA **4d** as the best candidate due to its high reactivity and selectivity, we performed the reactions with catalysts **2c**–**h** (Table 1, entries 6–10). Catalyst **2c**, which differs from **2b** in that it lacks the *p*-nitro substitution in the aromatic ring, unexpectedly showed no catalytic ability in the production of **5d**, with the dimerization of **4d** being the only reaction observed (Table 1, entry 6). On the other hand, catalyst **2d**, differing from **2a** by the change of the highly electron-withdrawing CCl_3 group to the mildly electron-donating and slightly less sterically demanding CH_3, furnished a reaction with formation of inseparable byproducts (Table 1, entry 7 vs. entry 5) and a worse stereoselection that that observed with **2a**. This last observation is probably attributable to the reduced acidity of NH in **2d** with respect to **2a**, leading to lower stereocontrol in the proton transfer step (see the above discussion).

Thus, catalysts **2f**–**h** furnished product **5d** with appreciable *ee* values but in low yields (Table 1, entries 8–10), and it was far from clear which catalytic species was involved. In fact, NMR analysis of samples taken directly from the reaction provided evidence that compounds **2f**–**h**, in contrast to the other catalysts, are unstable even in the absence of water or other deleterious impurities, and can easily decompose to β-isocupreidine (**1**) by reaction with the MBH adduct itself. Thus, the good enantioselection is very probably due to the intervention of both the original catalysts **2f**–**h** and β-ICD (**1**).

Encouraged by these results, our attention focused on catalyst **2a** and we carried out a comparison with β-isocupreidine (**1**; Table 2).

We used both DMNPA (**4d**) and the well-known and effective hexafluoroisopropyl acrylate (HFIPA; **4e**). In reactions with acrylate **4d**, the differences in stereocontrol between **1** and **2a** at all the temperatures were very low, whereas the yields were improved in the case of **2a** by about

Table 2. Synthesis of adducts **5d** and **5e**; comparison between catalysts **1** and **2a**.



3a **4d** or **4e** **5d** or **5e**

4d: R^3 = 2,6-$(CH_3)_2$-4-NO_2-C_6H_2; **4e**: R^3 = $(CF_3)_2CH$

Entry[a]	4	Cat	*T* [°C]	*t*	Yield, %[b] (*ee*, %)[c]
1	**4d**	**1**	0	18 h	33 (88)
2	**4d**	**1**	–18	3 d	50 (96)
3	**4d**	**2a**	–18	3 d	55 (97)
4	**4d**	**1**	–35	2 d	45 (98)
5	**4d**	**2a**	–35	3 d	58 (99)
6	**4e**	**1**	0	4 h	52 (81)
7	**4e**	**2a**	0	1 h	65 (88)

[a] Reagents and conditions (1 mmol scale): aldehyde, acrylate (1 equiv.), catalyst (10 mol-%), anhydrous DMF (0.3 mL). [b] Yield of pure isolated product. [c] Determined by HPLC analysis.

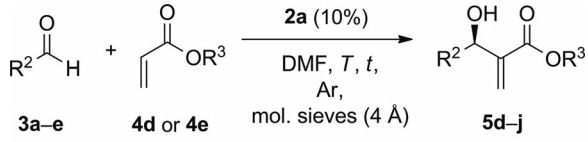
5–8% (Table 2, entry 1 vs. Table 1, entry 5, and Table 2, entries 2 vs. 3, and entries 4 vs. 5). The very similar behaviour of **1** and **2a** was also evident in the lower conversions and yields obtained at the higher temperature (0 °C), caused in both cases by the rapid production of the undesired dioxanone and then of the acidic 2,6-dimethyl-4-nitrophenol. In addition, when acrylate **4e** (HFIPA) was used together with catalyst **2a** at 0 °C, increased yield in a shorter reaction time and higher *ee* values were observed that those obtained with catalyst **1** (Table 2, entries 6 and 7).

The usefulness of the enantioselective Morita–Baylis–Hillman reaction catalyzed by **2a** was next examined at the lowest temperatures compatible with sustainable reaction times (Table 3). In fact, starting from aromatic aldehydes and exploiting DMNPA (**4d**), the corresponding adducts **5d**, **5f** and **5h** were obtained with an outstanding enantioselection (≥ 90% *ee*), whereas the yields were moderate but were not sensitive to the electronic properties of the aromatic ring, the presence of strong (NO_2) or moderately electron-withdrawing (Cl) groups being well-tolerated.

Contrary to our expectations, the reaction with the highly reactive 4-nitrobenzaldehyde was relatively sluggish in comparison with the reaction with benzaldehyde at the same temperature (–35 °C), whereas 4-chlorobenzaldehyde required a temperature of 0 °C to proceed within a reasonable time (Table 3, entries 3 and 5). This was caused by their low solubility, concomitant with a reduced solubility of acrylate **4d** at the lowest temperatures, and by the significant negative impact in the rate law (second order in aldehyde and first order in acrylate[9c]) of the actual concentrations. In fact, with these aldehydes, the dilution of the reaction caused a beneficial effect on the rate (see notes in Table 3).

It is noteworthy that adducts **5d**, **5f** and **5h** are all solids and were easily purified by fractional crystallization (data in square brackets, Table 3), and *ee* values in excess of 98% were always obtained, albeit with a further decrease in the final yields (39–52%).

Table 3. Synthesis of MBH adducts **5d–j** catalyzed by **2a**.



3a–e **4d** or **4e** **5d–j**

3a: R^2 = C_6H_5; **3b**: R^2 = 4-NO_2-C_6H_4; **3c**: R^2 = 4-Cl-C_6H_4;
3d: R^2 = CH_3CH_2; **3e**: R^2 = $(CH_3)_2CH$
4d: R^3 = 2,6-$(CH_3)_2$-4-NO_2-C_6H_2; **4e**: R^3 = $(CF_3)_2CH$

Entry[a]	3	4	*T* [°C]	*t*	Product	Yield, %[b] (*ee*, %)[c]
1	**3a**	**4d**	–35	3 d	**5d**	58 (99) [52, 100][d]
2	**3a**	**4e**	–55	3 h	**5e**	83 (98)[e]
3	**3b**	**4d**	–35	18 h	**5f**	48 (94)[f,g] [39, 99][d]
4	**3b**	**4e**	–55	2 h	**5g**	63 (91)[h,i]
5	**3c**	**4d**	0	4 d	**5h**	53 (90)[j] [43, 98][d]
6	**3d**	**4d**	–35	18 h	**5i**	46 (99)
7	**3e**	**4d**	–18	4 d	**5j**	43 (95)[k]

[a] Reagents and conditions (1 mmol scale): aldehyde, acrylate (1 equiv.), catalyst (10 mol-%), anhydrous DMF (0.3 mL). [b] Yield of pure isolated product. [c] Determined by HPLC analysis. [d] Yields and *ee* values, respectively, after fractional crystallization. [e] The corresponding (*R*,*R*)-*cis*-dioxanone was obtained in 5% yield and 45% *ee*. [f] DMF (1 mL) was used. [g] The corresponding (*R*,*R*)-*cis*-dioxanone was obtained in 11% yield and 49% *ee*. [h] DMF (2 mL) was used. [i] The corresponding (*R*,*R*)-*cis*-dioxanone was obtained in 14% yield and 16% *ee*. [j] DMF (0.5 mL) was used. [k] The corresponding dioxanone was obtained in 5% yield and 29% *ee* (*cis*/*trans* ratio 45:55).

The reactions of aldehydes **3a** and **3b** with HFIPA, carried out at the same temperature (–55 °C, Table 3, entries 2 and 4) as Hatakeyama's original and improved methods, furnished the MBH adduct **5e** with better results with respect to both β-ICD and HFIPA methodologies,[5a,5d] with 98% *ee* and 83% yield being achieved in only three hours, whereas adduct **5g** was obtained in 91% *ee* and 63% yield after two hours; a result that was intermediate between those of the original and the improved β-ICD/HFIPA methods.

When DMNPA was used in conjunction with linear and α-branched aldehydes, **3d** and **3e** (Table 3, entries 6 and 7), the corresponding adducts **5i** and **5j** where obtained with a greater (99 vs. 97% *ee*) or a lesser selectivity (95 vs. 99% *ee*), respectively, compared to the use of the β-ICD/HFIPA couple, but with a substantial decrease in the amount of dioxanone byproducts formed.[5a]

From the data reported, it is then evident that catalyst **2a**, when used in conjunction with either acrylate DMNPA (**4d**) or HFIPA (**4e**), shows an efficacy comparable, and sometimes slightly superior to that of the parent β-isocupreidine (**1**). In addition, the new and easily synthesised acrylate DMNPA allows selectivities to be obtained that are equal to or better than HFIPA, albeit with slightly lower yields, using both catalysts **1** and **2a**.

The absolute configuration of the previously unknown adducts **5a**, **5c**, **5d**, **5f** and **5h–j** generated by using **2a** as

catalyst was determined as *R* after conversion into the corresponding methyl esters and comparison of their optical rotation with literature data.

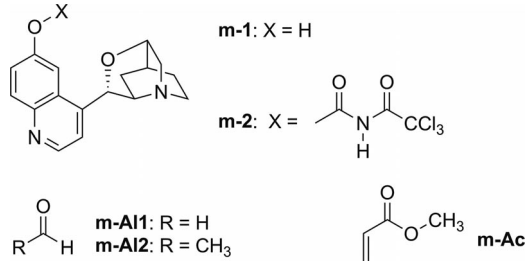
Mechanistic Considerations

In addition to ascertaining the effectiveness of the present methodology, many other important experimental observations can be made: (i) Chiral HPLC analysis of all the reactions reported here revealed no detectable change in the enantiomeric excess of the products during the entire reaction time. Thus, under these experimental conditions and for the time of interest, the reactions proceed under kinetic control; (ii) The preceding observation of a time-independent enantioselection also ruled out, in this case, both a mechanistic shift of the rate-determining proton-transfer step (from McQuade to Aggarwal models or vice versa) and an intervention of the MBH adduct itself in the transition states when the conversion proceeds. Considering that the two mechanisms have a different order in the rate law with respect to the aldehyde,[9b,9c,9e,9f] it is also clear from the observed constant proportion of reactants over the entire course of the reaction that, in this case, a change in the stereoselection from that of the McQuade pathway in the initial phase, to that of the Aggarwal pathway in the late stage is unlikely.[12] Thus, it can be safely assumed that only one mechanism is operating; (iii) The formation of dioxanones from reactive aldehydes and acrylates with a good leaving group suggests that, for these cases, the only operating mechanism is the McQuade non-alcohol-catalyzed process, with two molecules of aldehyde in the rate-determining step (Scheme 2, TSs **A** and **C**). In fact, the formation of dioxanone could theoretically occur even on the MBH adduct itself, but, in this case, a change in the ratio [MBH]/[dioxanone] and also in the *ee* of the MBH adduct would be expected as the reaction proceeded, as a result of two consecutive reactions. However, as stated before, the *ee* values were constant and, in addition, NMR analysis performed on same samples taken during the reaction clearly showed that no change in the ratio between the concentration of the MBH adducts and the dioxanones occurred. These experimental findings are only consistent with two parallel irreversible reactions; a McQuade mechanism seems very likely, in which the two observed products originate from the same common hemiacetalic intermediate; (iv) A very fine tuning of the electronic and steric properties of the acidic arm in the catalyst, starting from the common β-ICD skeleton, is essential for effective discrimination between the eight possible, rapidly equilibrating, diastereomers of the hemiacetal species. In particular, it appears that an excessively acidic moiety strongly decreases, or even suppresses, the catalytic activity. In the opposite case, a weak interaction with the negatively charged hemiacetalic oxygen can cause a loss in the directing effect on the preferred conformation of the six-membered proton transfer TSs (Scheme 2, TS **C**), that is responsible for the effectiveness of the kinetic resolution. Concerning the bulkiness of the R^1 substituent in catalysts **2a**–**h**, it seems clear that, in the case of acylic groups, a large steric encumbrance such as that of a phenyl group is sufficient to prevent the reaction, however, it is not clear at which step this occurs.

Having demonstrated, with a high degree of confidence, the mechanism operating in the rate-determining step, we started a computational investigation to obtain information on the real geometry of the transition states and then to shed light, at least qualitatively, on the interaction between the catalyst moiety and the remaining part of the reactant complex.

Computational Investigation

Recent computational investigations have aimed to elucidate the nature of the rate-determining step under different experimental conditions; all used high levels of theory and considered the solvent, at least as bulk, to obtain a quantitative energetic description of the entire mechanism.[9d,9f,9g,9j,9k] Simplified model systems were used to reduce the computational effort; thus model catalysts, aldehydes and acrylate were used (Scheme 3).

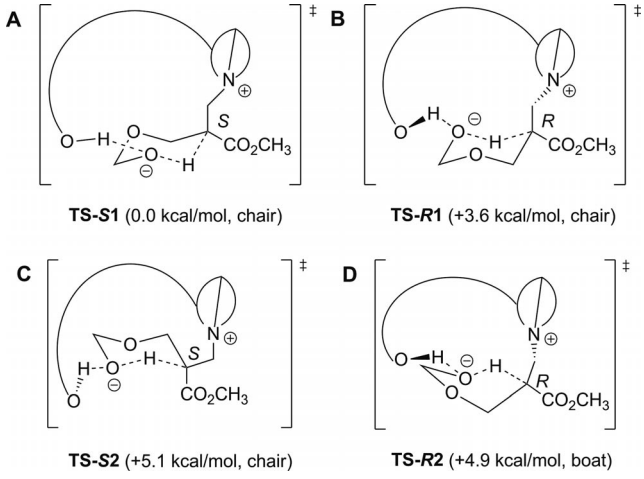


Scheme 3. Model compounds.

We used the AM1[14–15] semiempirical method to undertake a preliminary search of McQuade's proton transfer transition states obtained from the model compounds and confirmed that Aggarwal's TSs could not be identified under these conditions. The model structures were then refined with DFT computations using the hybrid functional M06–2X.[16] To take into account bulk solvent effects, full geometry optimizations within a continuum solvent model (with *N*,*N*-dimethylformamide as solvent) were carried out by applying the self-consistent reaction field (SCRF) approach, using the polarizable continuum model (IEF-PCM) method.[17] Given the system's dimension and the number of TSs to calculate, the 6-31G(d) basis set was used for atoms that have a prominent influence in determining the stereoselection, whereas the 3-21G* basis set was used to calculate the remaining atoms (see the Supporting Information for a detailed description). Finally, single point calculations with the 6-311++G(d,p) basis set were executed on all the computed TS structures; the resulting values are used in the following discussion on the the energetics of the systems (see below).

Initially, we searched the expected four hydrogen bonded[18] chair TSs obtained from catalyst **m-1**, methyl

acrylate (**m-Ac**) and two molecules of formaldehyde (**m-Al1**), starting from structures in which the methyleneisocupreidinium group lies in either an axial or an equatorial conformation and the carbon losing the transferred proton as either *R* or *S* configuration (Scheme 4).



Scheme 4. Model transition states computed for the McQuade proton transfer obtained from **m-Al1**, **m-Ac** and **m-1**.

In spite of many attempts, starting from a chair with an equatorial methyleneisocupreidinium group conformation and the *R* configuration at the carbon losing the proton, the minimization process invariably distorted the initial structures to the boat conformation **TS-*R*2**, whereas in all the other cases the expected chair structures were obtained.

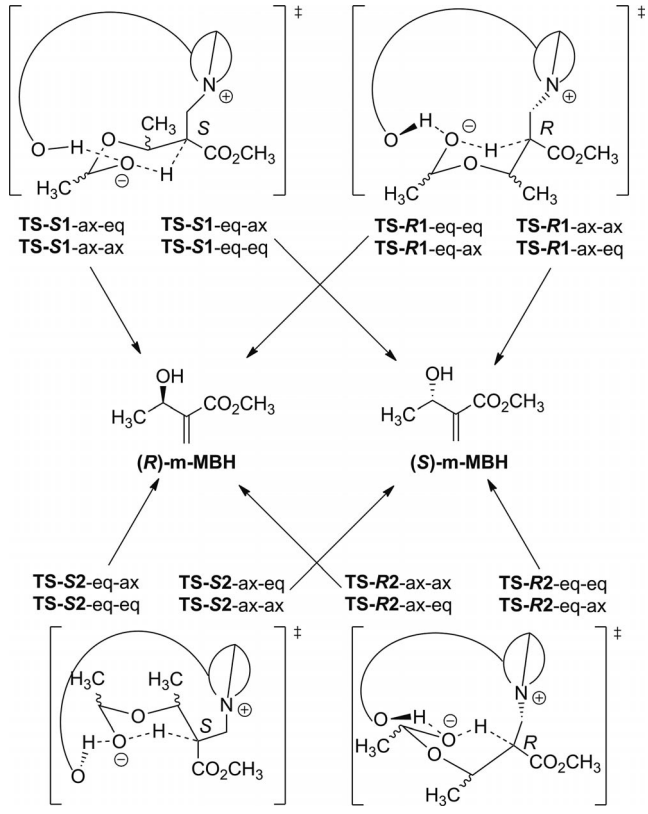
Modifying the four previous structures by addition of the two methyl groups in any of the possible combinations, we evaluated the stability and the steric features of all sixteen model TSs arising from substitution of acetaldehyde, **m-Al2**, in place of formaldehyde, **m-Al1** (Scheme 5).

The descriptors *R* and *S* again refer to the configuration of the carbon losing the transferred proton – the α-carbon with respect to the ester – whereas the other conformations (with the ax or eq inscription) indicate the orientation in the chair of the two methyl groups, starting from the one closest to the ester functionality.

The relative energies reported in Table 4 are in very good agreement with the experimentally observed enantioselectivity. In fact, **TS-*R*1**-eq-eq is by far the more stable transition state (Table 4, entry 1); this conformation has an axial methyleneisocupreidinium group, *R* configuration at the α-carbon, and both the methyl groups adopt equatorial orientations.

It is readily apparent from Figure 1 that the preferred proton transfer occurs through a chair conformation that lacks destabilizing steric interactions both between the chair substituents, and between the chair substituents and the catalyst moiety.

Two others TSs (Table 4, entries 2 and 11) also contribute to the overall predominance of the *R* enantiomer, whereas the only significant structure giving the *S* enantiomer (Table 4, **TS-*R*2**-eq-eq, entry 9 and Figure 2) lies 2.0 kcal/mol above the global minimum (**TS-*R*1**-eq-eq; Table 4, entry 1). The contribution of all the other TSs to the formation of both the enantiomers of the *m*-MBH adduct was found to be negligible.



Scheme 5. Model transition states computed for the McQuade proton transfer obtained from **m-Al2**, **m-Ac** and **m-1**.

Table 4. Relative energies of the model transition states with model catalyst **m-1**.

Entry	Model TS	Configuration of Model MBH[a]	Relative *E* [kcal/mol][b]
1	**TS-*R*1**-eq-eq	*R*	0.0
2	**TS-*R*1**-eq-ax	*R*	+1.5
3	**TS-*S*1**-eq-eq	*S*	+8.5
4	**TS-*S*1**-eq-ax	*S*	+6.5
5	**TS-*R*1**-ax-eq	*S*	+5.2
6	**TS-*R*1**-ax-ax	*S*	+8.3
7	**TS-*S*1**-ax-eq	*R*	+5.9
8	**TS-*S*1**-ax-ax	*R*	+7.7
9	**TS-*R*2**-eq-eq	*S*	+2.0
10	**TS-*R*2**-eq-ax	*S*	+4.4
11	**TS-*S*2**-eq-eq	*R*	+1.9
12	**TS-*S*2**-eq-ax	*R*	+4.6
13	**TS-*R*2**-ax-eq	*R*	+5.3
14	**TS-*R*2**-ax-ax	*R*	+9.0
15	**TS-*S*2**-ax-eq	*S*	+5.5
16	**TS-*S*2**-ax-ax	*S*	+9.6

[a] Configuration of the model MBH adduct after the hemiacetal decomposition. [b] Energies relative to the more stable transition state.

The very high energy of **TS-*S*1**-eq-eq (Table 4, entry 3) may seem surprising, considering the stability of the parent **TS-*S*1** with formaldehyde (Scheme 4) and the diequatorial arrangement of the methyl groups, but an inspection of its

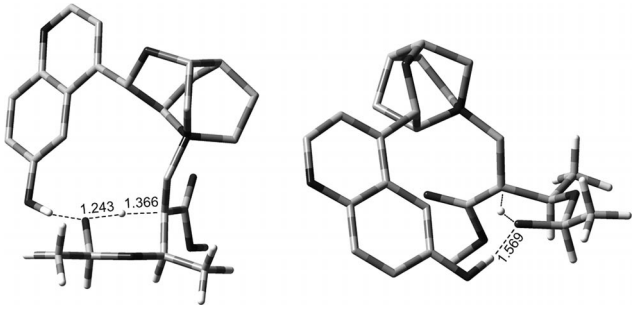


Figure 1. Different views of **TS-*R*1**-eq-eq with catalyst **m-1** (distances in angstroms [Å]; unnecessary hydrogen atoms omitted for clarity).

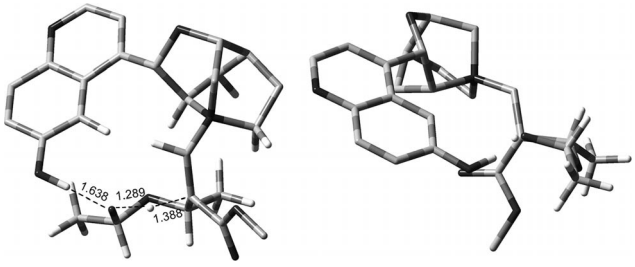


Figure 2. **TS-*S*1**-eq-eq (left) and **TS-*R*2**-eq-eq (right) with catalyst **m-1** (distances in angstroms [Å], unnecessary hydrogen atoms omitted for clarity).

structure clearly reveals that both the methyl groups suffer destabilizing steric interactions with the aromatic portion of the catalyst and, even more, with the hydrogen atoms of the quinuclidine cage (Figure 2).

In fact, these interactions are so strong that any change in the disposition of the methyl groups in the other **TS-*S*1**-derived transition states causes a stabilization (Table 4, entries 4, 7 and 8 vs. entry 3).

It can reasonably be assumed that the formation of the small amount of the *S* enantiomer experimentally observed may be due only to **TS-*R*2**-eq-eq (Figure 2), in which the equatorial methyl groups do not suffer any steric interactions but the arrangement of the six-membered cycle is almost identical to that of the intrinsically less stable boat structure of the parent **TS-*R*2** with formaldehyde (Scheme 4).

We recomputed all the model TSs using **m-2** as catalyst to evaluate if the different acidity and the longest spanning of its NH, with respect to the OH of **m-1**, could impose a reasonable distortion (or even a complete change) in the structures and lead to a variation in the energetics of the proton transfer TSs (Table 5). To ensure that the most stable structures were computed, many different initial dispositions of the acidic arm were tried for **TS-*R*1**-eq-eq, **TS-*S*1**-eq-eq, **TS-*R*2**-eq-eq and **TS-*S*2**-eq-eq, then all the other TSs were obtained by including appropriate changes to the methyl substituents in the six-membered cycle.

Table 5. Relative energies of the model transition states with model catalyst **m-2**.

Entry	Model TS	Configuration of Model MBH[a]	Relative *E* [kcal/mol][b]
1	**TS-*R*1**-eq-eq	*R*	0.0
2	**TS-*R*1**-eq-ax	*R*	+1.4
3	**TS-*S*1**-eq-eq	*S*	+6.2
4	**TS-*S*1**-eq-ax	*S*	+4.0
5	**TS-*R*1**-ax-eq	*S*	+4.6
6	**TS-*R*1**-ax-ax	*S*	+7.7
7	**TS-*S*1**-ax-eq	*R*	+6.4
8	**TS-*S*1**-ax-ax	*R*	+8.1
9	**TS-*R*2**-eq-eq	*S*	+10.5
10	**TS-*R*2**-eq-ax	*S*	+11.5
11	**TS-*S*2**-eq-eq	*R*	+2.7
12	**TS-*S*2**-eq-ax	*R*	+3.8
13	**TS-*R*2**-ax-eq	*R*	+12.0
14	**TS-*R*2**-ax-ax	*R*	+15.1
15	**TS-*S*2**-ax-eq	*S*	+6.7
16	**TS-*S*2**-ax-ax	*S*	+9.9

[a] Configuration of the model MBH adduct after the hemiacetal decomposition. [b] Energies relative to the more stable transition state.

In spite of the distortions imposed by the change in the acidic moiety, the relative energies were found to be globally similar between catalysts **m-1** and **m-2**, with some exceptions. The preferred transition states leading to the *R* enantiomer still resulted from **TS-*R*1**-eq-eq, **TS-*R*1**-eq-ax and **TS-*S*2**-eq-eq, with relative energies that are very close to those obtained with catalyst **m-1** (compare entries 1, 2 and 11 in Tables 4 and 5); the most striking difference was found to be the very high energy of the four structures derived from **TS-*R*2**.

In particular, for catalyst **m-1**, the **TS-*R*2**-eq-eq structure represents by far the major contribution to the formation of the *S* enantiomer of the product, being 2.0 kcal/mol above the global minimum **TS-*R*1**-eq-eq, whereas for catalyst **m-2** this value becomes 10.5 kcal/mol (compare entry 9 in Table 4 and Table 5), thus completely ruling out **TS-*R*2**-eq-eq for the production of the small amount of the experimentally observed minor enantiomer. In effect, the only lowest energy TSs furnishing the *S* enantiomer in the reaction with **m-2** catalyst are **TS-*S*1**-eq-ax (+4.0 kcal/mol; Table 5, entry 4) and **TS-*R*1**-ax-eq (+4.6 kcal/mol; Table 5, entry 5), which are more stable with respect to their counterparts with catalyst **m-1**. These energy differences are in reasonably good agreement with the excellent 99% *ee* obtained in the reaction with a linear aliphatic aldehyde (propionaldehyde; Table 3, entry 6) and catalyst **2a**.

It was also interesting to note that, as expected, the acidic arm of catalyst **m-2** imposes a significant distortion on the transition states with respect to the OH of **m-1**, as exemplified by the superimposition of the respective **TS-*R*1**-eq-eq structures shown in Figure 3.

Whereas the tricyclic cages of the catalysts and the two carbon atoms directly attached to them are practically coincident in both the **TS-*R*1**-eq-eq structures, the bond connecting the cage nitrogen and the adjacent exocyclic methylene is rotated by –120° upon changing from **m-1** to **m-2**.

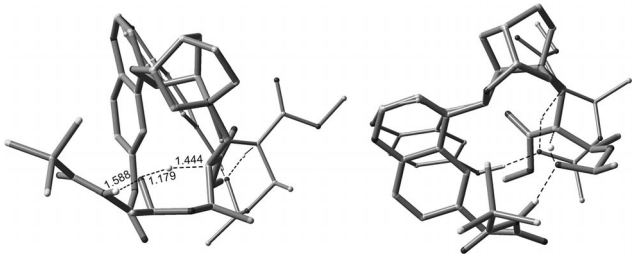


Figure 3. Different views of the superimposition of **TS-*R*1**-eq-eq with catalyst **m-1** (ball and stick with radii scaled by 20%) and catalyst **m-2** (tube). Distances are in angstroms [Å], and all hydrogen atoms, except the transferred protons and the OH or NH protons, are omitted for clarity.

This variation in the final positioning of the chair structure is partially counterbalanced by the rotation of the bond connecting the same methylene group and the subsequent α-carbon (+86°). Moreover, the aromatic moiety in **TS-*R*1**-eq-eq with catalyst **m-2** is rotated by +33°, with respect to that with catalyst **m-1**, and a detailed visual inspection also revealed that, in this case, the TS structure is not a perfect chair but is slightly twisted.

Conclusions

We report here an improved asymmetric Morita–Baylis–Hillman reaction that exploits the new difunctional catalyst **2a** and the new 2,6-dimethyl-4-nitrophenyl acrylate (DMNPA; **4d**). Moreover, identification of the reaction mechanism, supported by experimental data and computational investigations, has shed light on the reasons behind the enantioselectivity observed with catalysts **1** (β-ICD) and **2a**. Novel β-isocupreidine derivatives are under study as catalysts, both theoretically and experimentally, and results will be reported in due course.

Experimental Section

General Methods: Melting points were measured with an Electrothermal IA 9000 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, with a Varian Gemini 200 spectrometer in $CDCl_3$ at 25 °C. Chemical shifts are reported in ppm relative to residual solvent signals (δ =7.26 and 77.0 ppm for ^{1}H and ^{13}C NMR, respectively), and coupling constants (J) are given in Hz. LC electrospray ionization mass spectra were obtained with an Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Specific rotation measurements {$[a]_D^{25}$} were recorded at room temperature with a Perkin–Elmer Model 241 polarimeter at the sodium D line (concentration given in g/100 mL). Elemental analyses were performed with a Carlo Erba CHN Elemental Analyzer. The *ee* values of Morita–Baylis–Hillman adducts were verified by HPLC analysis, eluting solutions with a concentration between 0.02 and 0.2 mg/mL in a Hewlett–Packard 1100 chromatograph equipped with a Daicel Chiralcel OD-H column and a diode-array UV detector (210, 230 and 250 nm). To obtain reliable results, even in the case of solid compounds, before HPLC analysis all the product was completely dissolved in 2-propanol until a clear homogeneous solution was obtained, then a suitable aliquot was diluted with *n*-hexane to the desired concentration. The absolute configuration of the Morita–Baylis–Hillman adducts **5**, or of their methyl derivatives, were determined by comparison of their optical rotation with literature values, except in the case of product **5h**, the *R*-configuration of which was assumed by chemical analogy.

Materials: Analytical and HPLC-grade solvents for workup and purification procedures and HPLC analysis were purchased from commercial suppliers and used as received. Anhydrous methanol was purchased from Aldrich. Anhydrous CH_2Cl_2 and DMF were obtained, respectively, by distillation over CaH_2 and P_4O_{10}, then stored over 4 Å molecular sieves under an inert atmosphere for a maximum of one month. Benzaldehyde, propionaldehyde and isobutyraldehyde were purified by distillation at atmospheric pressure, *p*-chlorobenzaldehyde was sublimated twice (50 °C/2 Torr) and *p*-nitrobenzaldehyde was dissolved in CH_2Cl_2 and passed through a short column of basic aluminium oxide, then concentrated. All aldehydes were stored, tightly capped, under an inert atmosphere for a maximum of one (benzaldehyde, propionaldehyde and isobutyraldehyde) or five months (*p*-nitro- and *p*-chlorobenzaldehyde). Hexafluoroisopropyl acrylate (HFIPA) was purchased from Aldrich and used as received. Racemic samples of MBH adducts were prepared by using DABCO as the catalyst at room temperature. β-ICD was synthesized following a literature procedure.[5a] Trichloroacetyl isocyanate was purchased from Aldrich and used as received; other isocyanates and acyl isocyanates were prepared according to the literature.[8] Column chromatography was performed with Kieselgel 60 (Merck, 230–400 mesh ASTM). TLC analysis was performed with Fluka silica gel TLC-PET foil. TLC plates were analyzed by exposure to UV light and by submersion in an aqueous $KMnO_4$ solution, followed by heating.

General Procedure for the Preparation of Catalysts 2a–h: To a solution of β-isocupreidine (2 mmol) in anhydrous CH_2Cl_2 (4 mL) under an inert atmosphere, the appropriate isocyanate (3 mmol) or acyl isocyanate (2.2 mmol) was added at room temperature. The reaction was stirred for the appropriate time (see below) and then directly submitted to chromatographic purification (CH_2Cl_2/MeOH), to give the pure product, except in the case of **2b** and **2e**, which were inseparable from by-products.

Caution: All the products, in particular **2b** and **2e**–**h**, can undergo slow methanolysis, especially at the end of the evaporation, and must be concentrated at room temperature. The yields and purities were slightly improved when the evaporation was stopped when the products started to become viscous, then a small amount of CH_2Cl_2 was added and the product was finally concentrated. The pure products are sensitive to moisture and carbon dioxide and must be stored tightly capped and under an inert atmosphere if extended preservation is desired.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl (2,2,2-Trichloroacetyl)carbamate (2a): Following the general procedure (1 h reaction time) the title compound was obtained in 85% yield as a brownish amorphous solid; m.p. 185–190 °C (dec.). $[a]_D^{25}$ = –21.1 (*c* = 0.71, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.3 Hz, 3 H), 1.60 (dd, *J* = 6.4, 13.4 Hz, 1 H), 1.81 (q, *J* = 7.3 Hz, 2 H), 1.93–2.14 (m, 3 H), 2.48–2.51 (m, 1 H), 3.16 (d, *J* = 14.1 Hz, 1 H), 3.43–3.53 (m, 2 H), 4.18 (d, *J* = 14.1 Hz, 1 H), 4.32 (d, *J* = 6.4 Hz, 1 H), 6.05 (s, 1 H), 7.30 (dd, *J* = 2.4, 9.1 Hz, 1 H), 7.56 (d, *J* = 4.4 Hz, 1 H), 7.92 (d, *J* = 2.4 Hz, 1 H), 7.96 (d, *J* = 9.1 Hz, 1 H), 8.73 (d, *J* = 4.4 Hz, 1 H), 9.40 (br. s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.0, 21.1, 21.3, 27.0, 32.1, 46.1, 53.5, 58.9, 71.1, 75.8, 103.7, 118.5, 122.2, 125.9, 131.6, 138.0, 143.2, 146.5, 156.8, 165.2 ppm. ESI-MS: *m*/*z* = 498 [M(3 × ^{35}Cl) + H]$^+$, 500 [M(2 × ^{35}Cl, 1 × ^{37}Cl) + H]$^+$. $C_{22}H_{22}Cl_3N_3O_4$

(498.79): calcd. C 52.98, H 4.45, N 8.42; found C 53.00, H 4.50, N 8.36.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl (4-Nitrobenzoyl)carbamate (2b): Following the general procedure (2 h reaction time) the title compound was obtained in 55% yield as a brownish amorphous solid (a preliminary elution with ethyl acetate was necessary before eluting with CH_2Cl_2/MeOH); m.p. 152–158 °C (dec.). $[\alpha]_D^{25}$ = –48.7 (*c* = 0.55, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.3 Hz, 3 H), 1.29 (dd, *J* = 6.2, 13.4 Hz, 1 H), 1.48–1.82 (m, 5 H), 2.15–2.19 (m, 1 H), 2.69 (d, *J* = 13.8 Hz, 1 H), 2.98–3.04 (m, 2 H), 3.54 (d, *J* = 4.9 Hz, 1 H), 3.58 (d, *J* = 13.8 Hz, 1 H), 5.98 (s, 1 H), 7.58 (dd, *J* = 2.4, 9.1 Hz, 1 H), 7.81 (d, *J* = 4.4 Hz, 1 H), 7.87 (d, *J* = 2.4 Hz, 1 H), 8.21 (d, *J* = 9.1 Hz, 1 H), 8.35–8.39 (m, 4 H), 8.95 (d, *J* = 4.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.2, 23.3, 23.9, 27.3, 32.8, 46.6, 54.6, 56.8, 72.9, 77.3, 114.0, 119.7, 123.7, 124.0, 125.9, 131.4, 132.2, 134.6, 144.3, 146.2, 148.4, 150.3, 151.0, 163.4 ppm. ESI-MS: *m*/*z* = 503 [M + H]$^+$. $C_{27}H_{26}N_4O_6$ (502.53): calcd. C 64.53, H 5.22, N 11.15; found C 64.60, H 5.31, N 11.08.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl Benzoylcarbamate (2c): Following the general procedure (8 h reaction time) the title compound was obtained in a crude yield of 68% (not separated from byproducts), as a brownish waxy solid. $[\alpha]_D^{25}$ = –15.8 (*c* = 1.32, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H), 1.36 (dd, *J* = 6.2, 13.4 Hz, 1 H), 1.62–1.77 (m, 4 H), 1.85 (dd, *J* = 6.2, 13.4 Hz, 1 H), 2.22–2.27 (m, 1 H), 2.76 (d, *J* = 13.8 Hz, 1 H), 3.10–3.16 (m, 2 H), 3.71–3.80 (m, 2 H), 6.12 (s, 1 H), 7.40–7.68 (m, 5 H), 7.78 (d, *J* = 4.4 Hz, 1 H), 7.96 (d, *J* = 2.4 Hz, 1 H), 8.18–8.27 (m, 3 H), 8.94 (d, *J* = 4.4 Hz, 1 H) ppm. ESI-MS: *m*/*z* = 458 [M + H]$^+$. $C_{27}H_{27}N_3O_4$ (457.53): calcd. C 70.88, H 5.95, N 9.18; found C 70.91, H 6.01, N 9.11.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl Acetylcarbamate (2d): Following the general procedure (5 h reaction time) the title compound was obtained in 57% yield as a pale-yellow solid; m.p. 166–169 °C (dec.). $[\alpha]_D^{25}$ = –6.5 (*c* = 1.47, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3 H), 1.19 (dd, *J* = 6.4, 12.2 Hz, 1 H), 1.41–1.72 (m, 5 H), 2.04–2.10 (m, 1 H), 2.30 (s, 3 H), 2.62 (d, *J* = 13.6 Hz, 1 H), 2.91–2.97 (m, 2 H), 3.40 (d, *J* = 6.2 Hz, 1 H), 3.47 (d, *J* = 13.6 Hz, 1 H), 5.88 (s, 1 H), 7.40 (dd, *J* = 2.4, 9.1 Hz, 1 H), 7.59 (d, *J* = 2.4 Hz, 1 H), 7.73 (d, *J* = 4.5 Hz, 1 H), 8.10 (d, *J* = 9.1 Hz, 1 H), 8.87 (d, *J* = 4.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.2, 21.0, 23.5, 24.6, 27.3, 32.8, 46.7, 54.8, 56.6, 73.0, 77.2, 113.7, 119.4, 124.3, 125.7, 131.8, 144.5, 146.0, 148.5, 149.9, 169.3 ppm. ESI-MS: *m*/*z* = 396 [M + H]$^+$. $C_{22}H_{25}N_3O_4$ (395.46): calcd. C 66.82, H 6.37, N 10.63; found C 66.85, H 6.42, N 10.62.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl Benzylcarbamate (2e): Following the general procedure (24 h reaction time) the title compound was obtained in a crude yield of 70% (not separated from byproducts), as a yellow waxy solid. $[\alpha]_D^{25}$ = –1.5 (*c* = 1.78, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H), 1.33 (dd, *J* = 6.4, 12.2 Hz, 1 H), 1.55–1.86 (m, 5 H), 2.20–2.25 (m, 1 H), 2.75 (d, *J* = 13.6 Hz, 1 H), 3.03–3.11 (m, 2 H), 3.67–3.76 (m, 2 H), 4.50 (d, *J* = 6.8 Hz, 2 H), 5.95 (t, *J* = 6.8 Hz, 1 H), 6.03 (s, 1 H), 7.29–7.41 (m, 5 H), 7.56 (dd, *J* = 2.1, 9.1 Hz, 1 H), 7.74 (d, *J* = 4.4 Hz, 1 H), 7.87 (d, *J* = 2.1 Hz, 1 H), 8.13 (d, *J* = 9.1 Hz, 1 H), 8.90 (d, *J* = 4.4 Hz, 1 H) ppm. ESI-MS: *m*/*z* = 444 [M + H]$^+$. $C_{27}H_{29}N_3O_3$ (443.54): calcd. C 73.11, H 6.59, N 9.47; found C 73.23, H 6.68, N 9.37.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl [(*R*)-1-Phenylethyl]carbamate (2f): Following the general procedure (5 h reaction time) the title compound was obtained in 85% yield as a pale-yellow waxy solid. $[\alpha]_D^{25}$ = +81.1 (*c* = 0.88, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.3 Hz, 3 H), 1.15 (dd, *J* = 6.4, 12.2 Hz, 1 H), 1.38–1.72 (m, 5 H), 1.60 (d, *J* = 6.7 Hz, 3 H), 2.07–2.12 (m, 1 H), 2.58 (d, *J* = 13.6 Hz, 1 H), 2.67–2.82 (m, 2 H), 3.46 (d, *J* = 6.4 Hz, 1 H), 3.52 (d, *J* = 13.6 Hz, 1 H), 4.92 (dq, *J* = 6.7, 6.7 Hz, 1 H), 5.92 (s, 1 H), 7.15–7.50 (m, 6 H), 7.70–7.83 (m, 3 H), 8.06 (d, *J* = 9.1 Hz, 1 H), 8.83 (d, *J* = 4.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.2, 21.7, 23.4, 24.0, 27.3, 32.8, 46.2, 50.6, 54.4, 56.3, 72.9, 77.1, 114.0, 119.3, 124.4, 125.7, 126.3, 127.2, 128.5, 131.5, 142.9, 144.3, 145.7, 148.8, 149.6, 153.9 ppm. ESI-MS: *m*/*z* = 458 [M + H]$^+$. $C_{28}H_{31}N_3O_3$ (457.57): calcd. C 73.50, H 6.83, N 9.18; found C 73.55, H 6.86, N 9.14.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl [(*S*)-1-Phenylethyl]carbamate (2g): Following the general procedure (5 h reaction time) the title compound was obtained in 81% yield as a pale-yellow waxy solid. $[\alpha]_D^{25}$ = –86.2 (*c* = 1.02, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.3 Hz, 3 H), 1.23 (dd, *J* = 6.2, 12.8 Hz, 1 H), 1.60 (d, *J* = 6.7 Hz, 3 H), 1.55–1.83 (m, 5 H), 2.12–2.17 (m, 1 H), 2.65 (d, *J* = 13.7 Hz, 1 H), 2.85–3.01 (m, 2 H), 3.55–3.65 (m, 2 H), 4.99 (dq, *J* = 6.7, 6.7 Hz, 1 H), 5.90 (s, 1 H), 7.13–7.49 (m, 6 H), 7.55–7.62 (m, 1 H), 7.68 (d, *J* = 4.4 Hz, 1 H), 7.83 (d, *J* = 2.4 Hz, 1 H), 8.04 (d, *J* = 9.1 Hz, 1 H), 8.83 (d, *J* = 4.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.3, 22.1, 23.2, 23.6, 27.4, 46.2, 50.9, 54.2, 56.5, 72.6,77.1, 113.9, 119.3, 124.8, 125.7, 126.1, 127.4, 128.7, 131.6, 143.2, 143.8, 145.9, 149.0, 149.7, 153.8 ppm. ESI-MS: *m*/*z* = 458 [M + H]$^+$. $C_{28}H_{31}N_3O_3$ (457.57): calcd. C 73.50, H 6.83, N 9.18; found C 73.53, H 6.87, N 9.12.

4-[(5*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl]quinolin-6-yl (2-Benzamidoethyl)carbamate (2h): Following the general procedure (5 h reaction time) the title compound was obtained in 63% yield as a yellow waxy solid. $[\alpha]_D^{25}$ = –3.8 (*c* = 1.13, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.4 Hz, 3 H), 1.39–1.66 (m, 5 H), 2.04 (br. s, 1 H), 2.68 (d, *J* = 13.6 Hz, 1 H), 2.97–3.01 (m, 2 H), 3.22 (d, *J* = 5.5 Hz, 1 H), 3.45–3.80 (m, 5 H), 5.75 (s, 1 H), 6.75–6.83 (m, 2 H), 7.00–7.07 (m, 1 H), 7.40 (dd, *J* = 2.2, 9.1 Hz, 1 H), 7.49–7.57 (m, 3 H), 7.94 (d, *J* = 2.2 Hz, 1 H), 8.06–8.11 (m, 2 H), 8.76 (d, *J* = 4.5 Hz, 1 H), 9.61 (br. s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.1, 22.6, 22.8, 27.1, 32.5, 39.7, 40.3, 46.0, 53.8, 56.4, 71.9, 76.8, 114.7, 119.3, 124.5, 125.7, 126.7, 127.7, 130.8, 131.9, 133.1, 143.2, 145.7, 149.0, 149.5, 155.9, 167.2 ppm. ESI-MS: *m*/*z* = 501 [M + H]$^+$. $C_{29}H_{32}N_4O_4$ (500.60): calcd. C 69.58, H 6.44, N 11.19; found C 69.64, H 6.51, N 11.15.

General Procedure for the Preparation of Acrylates 4a–d: To a solution of the appropriate phenol or alcohol (20 mmol) dissolved in anhydrous CH_2Cl_2 (20 mL) under an inert atmosphere, TEA (3 mL, 21 mmol) and DMAP (250 mg, 2 mmol) were sequentially added. The reaction was brought to 0 °C with an ice bath, then acryloyl chloride (1.68 mL, 20 mmol) dissolved in CH_2Cl_2 (3 mL) was slowly added. After removal of the bath, the reaction was stirred for 24 h (8 h in the case of **4b** and **4d**) at room temperature, then the solvent was partially evaporated under vacuum and the residue was diluted with ethyl acetate (100 mL) and 0.2 M HCl (20 mL). After separation, the organic layer was washed with water (10 mL). The unified aqueous phases were further extracted with ethyl acetate (20 mL) and the second organic phase was washed with water (10 mL). The unified organic phases were dried with anhydrous Na_2SO_4 and concentrated under vacuum, and the residues were purified by silica gel chromatography (*c*-hexane/ethyl acetate) to give acrylates **4a**–**d**.

Mesityl Acrylate (4a): Starting from 2,4,6-trimethylphenol, the title compound was obtained in 78% yield as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 6 H), 2.28 (s, 3 H), 6.04 (dd, *J* =

1.5, 10.3 Hz, 1 H), 6.40 (dd, J = 10.3, 17.3 Hz, 1 H), 6.68 (dd, J = 1.5, 17.3 Hz, 1 H), 6.93 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.1, 20.7, 127.6, 129.1, 129.6, 132.1, 135.2, 145.7, 163.9 ppm. ESI-MS: m/z = 190 $[M]^+$. $C_{12}H_{14}O_2$ (190.24): calcd. C 75.76, H 7.42; found C 75.80, H 7.49.

Naphthalen-1-yl Acrylate (4b): Starting from 1-naphthol, the title compound was obtained in 86% yield as a colourless oil and identified by comparison of its ^{1}H NMR spectrum with the literature data.[19]

4-Nitrobenzyl Acrylate (4c): Starting from 4-nitrobenzyl alcohol, the title compound was obtained in 89% yield as a colourless oil that rapidly solidify to white crystals; m.p. 50–52 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.30 (s, 2 H), 5.92 (dd, J = 1.5, 10.3 Hz, 1 H), 6.20 (dd, J = 10.3, 17.2 Hz, 1 H), 6.50 (dd, J = 1.5, 17.2 Hz, 1 H), 7.50–7.57 (m, 2 H), 8.20–8.26 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 64.8, 123.8, 127.7, 128.4, 131.9, 143.1, 165.6 ppm. ESI-MS: m/z = 208 $[M + H]^+$. $C_{10}H_9NO_4$ (207.19): calcd. C 57.97, H 4.38, N 6.76; found C 58.00, H 4.40, N 6.71.

2,6-Dimethyl-4-nitrophenyl Acrylate (4d): Starting from 2,6-dimethyl-4-nitrophenol, the title compound was obtained in 97% yield as a white amorphous solid. Recrystallization from ethyl acetate furnished white crystals; m.p. 103–104 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.25 (s, 6 H), 6.12 (dd, J = 1.4, 10.3 Hz, 1 H), 6.38 (dd, J = 10.3, 17.2 Hz, 1 H), 6.70 (dd, J = 1.4, 17.2 Hz, 1 H), 7.98 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.4, 123.7, 126.6, 132.2, 133.7, 145.3, 152.9, 162.8 ppm. ESI-MS: m/z = 222 $[M + H]^+$. $C_{11}H_{11}NO_4$ (221.21): calcd. C 59.73, H 5.01, N 6.33; found C 59.77, H 5.06, N 6.30.

General Procedure for the Enantioselective Morita–Baylis–Hillman Reactions and for Conversion of Adducts 5a–h into Methyl Derivatives 6a–c: Catalyst **1** or **2** (0.1 mmol) was brought into a dried two-necked 5 mL flask by diluting a known amount with anhydrous CH_2Cl_2, then keeping a suitable aliquot and evaporating CH_2Cl_2. After drying of the catalyst by dissolution in anhydrous THF (0.5 mL) followed by evaporation and redissolution in anhydrous DMF (0.3 mL, unless otherwise noted), aldehyde **3** (1 mmol) and freshly activated powdered 4 Å molecular sieves (about 50 mg) were sequentially added. The mixture was stirred for 10 min at room temperature and cooled (thermostat control) in a cryogenic bath (or ice bath for reactions at 0 °C) for 20 min, then acrylate **4** (1 mmol) was slowly added. When the conversion [monitored by ^{1}H NMR analysis of samples taken directly from the reaction mixture (about 20 μL) and diluted in $CDCl_3$] stopped increasing, the reaction was quenched by addition of 0.1 M HCl (3 mL) and extracted with ethyl acetate (20 mL). The organic phase was successively washed with 0.1 M HCl (2 × 1 mL) and brine (2 mL). The unified aqueous phases were extracted with additional ethyl acetate (10 mL), which was washed with fresh 0.1 M HCl (2 × 1 mL) and brine (2 mL). The unified organic phases were dried with anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude residue by silica gel chromatography (*c*-hexane/ethyl acetate) furnished the pure Morita–Baylis–Hillman adducts **5a**–**h**. Conversion into the corresponding methyl esters was accomplished by dissolving adducts **5a**–**h** in anhydrous MeOH (1 mL), adding triethylamine (0.5 mL), and stirring at room temperature for 1 h (5 h for **5a** and **5c**). After evaporation of the volatiles under vacuum, the residue was purified by silica gel chromatography (*c*-hexane/ethyl acetate), to give the methyl esters in 80–95% yield.

(*R*)-Mesityl 2-[Hydroxy(phenyl)methyl]acrylate (5a): Following the general procedure (catalyst **2a**, –18 °C, 20 d) the title compound was obtained in 71% yield as a colourless oil that solidified upon standing. Recrystallization from *c*-hexane/ethyl acetate (2 crops) furnished colourless crystals in 55% final yield; m.p. 75–79 °C. The *ee* of the product was determined by HPLC using a Chiralcel OD-H column (*n*-hexane/2-propanol 9:1, flow rate 1.0 mL/min, λ = 210 nm): t_R = 6.9 (*R*), 7.6 (*S*) min; 85 and 98% *ee* before and after recrystallization, respectively. $[\alpha]_D^{25}$ = –26.3 (c = 0.95, CH_2Cl_2), 98% *ee*. The absolute configuration of compound **5a** was determined as (*R*) after conversion into the corresponding methyl ester and comparison of its optical rotation {$[\alpha]_D^{25}$ = –109.0 (c = 0.62, MeOH), 98% *ee*} with literature values {$[\alpha]_D^{18}$ = –109.3 (c = 0.45, MeOH), 95% *ee*.[5a] $[\alpha]_D^{18}$ = –111.1 (c = 1.11, MeOH)[13]}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.90 (s, 6 H), 2.25 (s, 3 H), 2.91 (br. s, 1 H), 5.67 (s, 1 H), 6.10 (s, 1 H), 6.62 (s, 1 H), 6.83 (s, 2 H), 7.22–7.45 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.8, 20.6, 73.1, 126.3, 126.7, 127.8, 128.3, 129.0, 129.5, 135.3, 141.2, 141.6, 145.4, 164.2. ESI-MS: m/z = 296 $[M]^+$. $C_{19}H_{20}O_3$ (296.37): calcd. C 77.00, H 6.80; found C 77.08, H 6.90.

(*R*)-Naphthalen-1-yl 2-[Hydroxy(phenyl)methyl]acrylate (5b): Following the general procedure (catalyst **2a**, –18 °C, 18 d) the title compound was obtained in 43% yield as a pale-yellow oil and identified by comparison of its NMR spectra with literature data.[10b] The *ee* of the product was determined by HPLC using a Chiralcel OD-H column (*n*-hexane/2-propanol 9:1, flow rate 1.0 mL/min, λ = 210 nm): t_R = 16.7 (*R*), 19.7 (*S*) min; 70% *ee*. $[\alpha]_D^{25}$ = –8.2 (c = 0.97, $CHCl_3$), 70% *ee*. The absolute configuration of compound **5b** was determined as (*R*) by comparison of its optical rotation with the literature value[10b] {$[\alpha]_D^{18}$ = +10.9 (c = 0.80, $CHCl_3$), 92% *ee*}.

(*R*)-4-Nitrobenzyl 2-[Hydroxy(phenyl)methyl]acrylate (5c): Following the general procedure (catalyst **2a**, –18 °C, 23 d) the title compound was obtained in 78% yield as a white amorphous solid. Recrystallization from CH_2Cl_2 furnished colourless crystals; m.p. 90–94 °C. The *ee* of the product was determined by HPLC using a Chiralcel OD-H column (*n*-hexane/*i*PrOH, 9:1, flow rate 1.0 mL/min, λ = 210 nm): t_R = 26.3 (*S*), = 28.7 (*R*) min; 45% *ee*. $[\alpha]_D^{25}$ = –9.6 (c = 1.77, $CHCl_3$); 45% *ee*. The absolute configuration of compound **5c** was determined as (*R*) after conversion into the corresponding methyl ester and comparison of its optical rotation {$[\alpha]_D^{25}$ = –50.7 (c = 1.03, MeOH), 45% *ee*} with the literature values {$[\alpha]_D^{18}$ = –109.3 (c = 0.45, MeOH), 95% *ee*[5a]; $[\alpha]_D^{18}$ = –111.1 (c = 1.11, MeOH)[13]}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.14 (br. s, 1 H), 5.13 (d, J = 13.6 Hz, 1 H), 5.22 (d, J = 13.6 Hz, 1 H), 5.56 (s, 1 H), 6.00 (s, 1 H), 6.43 (s, 1 H), 7.25–7.34 (m, 7 H), 8.09 (d, J = 8.7 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 64.8, 72.7, 123.5, 126.4, 126.6, 127.8, 127.9, 128.3, 141.1, 141.6, 142.7, 147.4, 165.4. ESI-MS: m/z = 313 $[M]^+$. $C_{17}H_{15}NO_5$ (313.31): calcd. C 65.17, H 4.83, N 4.47; found C 65.20, H 4.88, N 4.41.

(*R*)-2,6-Dimethyl-4-nitrophenyl 2-[Hydroxy(phenyl)methyl]acrylate (5d): Following the general procedure (catalyst **2a**, –35 °C, 3 d), the title compound was obtained in 58% yield as a white amorphous solid. Recrystallization from diethyl ether (3 crops) furnished the enantiopure product as white crystals in 52% final yield; m.p. 78–80 °C. The *ee* of the product was determined by HPLC using a Chiralcel OD-H column (*n*-hexane/*i*PrOH, 8:2; flow rate 0.25 mL/min; λ = 210 nm): t_R = 32.6 (*R*), 34.6 (*S*) min; 99 and 100% *ee* before and after recrystallization, respectively. $[\alpha]_D^{25}$ = –19.5 (c = 1.74, CH_2Cl_2); 99% *ee*. The absolute configuration of compound **5d** was determined as (*R*) after conversion into the corresponding methyl ester and comparison of its optical rotation {$[\alpha]_D^{25}$ = –110.9 (c = 1.23, MeOH); 100% *ee*} with the literature values {$[\alpha]_D^{18}$ = –109.3 (c = 0.45, MeOH); 95% *ee*[5a]; $[\alpha]_D^{18}$ = –111.1 (c = 1.11, MeOH)[13]}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.01 (s, 6 H), 2.60 (br. s, 1 H), 5.70 (s, 1 H), 6.24–6.25 (m, 1 H), 6.66–6.67 (m, 1 H),

7.27–7.47 (m, 5 H), 7.91 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.2, 73.0, 123.7, 126.8, 127.5, 128.3, 128.7, 132.2, 140.9, 141.1, 145.4, 152.7, 163.1 ppm. ESI-MS: m/z = 327 $[M]^+$. $C_{18}H_{17}NO_5$ (327.34): calcd. C 66.05, H 5.23, N 4.28; found C 66.09, H 5.29, N 4.20.

(*R*)-1,1,1,3,3,3-Hexafluoroprop-2-yl 2-[Hydroxy(phenyl)methyl]-acrylate (5e): Following the general procedure (catalyst **2a**, –55 °C, 3 h) the title compound was obtained in 83% yield as a colourless oil. The identity was verified by comparison of its ^{1}H NMR with literature data.[5a] The *ee* of the product was determined, on both **5e** and its methyl derivative, by HPLC using a Chiralcel OD-H column {**5e**: *n*-hexane/*i*PrOH, 99:1; flow rate 0.5 mL/min; λ = 210 nm: t_R = 23.0 (*S*), 25.2 (*R*) min; 98% *ee*; methyl derivative: *n*-hexane/*i*PrOH, 98:2; flow rate 0.7 mL/min; λ = 210 nm: t_R = 27.1 (*S*), 29.0 (*R*) min; 98% *ee*}. $[\alpha]_D^{25}$ = –54.8 (c = 1.15, $CHCl_3$); 98% *ee*. The absolute configuration of compound **5e** was determined as (*R*) by comparison of its optical rotation with the literature value {$[\alpha]_D^{22}$ = –53.2 (c = 1.045, $CHCl_3$); 95% *ee*[5a]}.

(*R*)-2,6-Dimethyl-4-nitrophenyl 2-[Hydroxy(4-nitrophenyl)methyl]-acrylate (5f): Following the general procedure (1 mL of DMF, catalyst **2a**, –35 °C, 18 h) the title compound was obtained in 48% yield as a yellow amorphous solid. Recrystallization from diethyl ether (3 crops) furnished almost enantiopure product as pale-yellow crystals in 39% final yield; m.p. 106–110 °C. The *ee* of the product was determined after derivatization to the corresponding methyl ester, by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*PrOH, 95:5, flow rate 0.7 mL/min, λ = 210 nm]: t_R = 32.2 (*R*), 35.3 (*S*) min; 94 and 99% *ee* before and after recrystallization, respectively. $[\alpha]_D^{25}$ = +8.1 (c = 1.30, CH_2Cl_2), 99% *ee*. The absolute configuration of compound **5f** was determined as (*R*) after conversion into the corresponding methyl ester and comparison of its optical rotation {$[\alpha]_D^{25}$ = –83.5 (c = 0.72, MeOH), 99% *ee*} with the literature value {$[\alpha]_D^{25}$ = –76.9 (c = 1.03, MeOH); 91% *ee*[5a]}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.08 (s, 6 H), 2.97 (br. d, J = 4.8 Hz, 1 H), 5.78 (br. d, J = 4.8 Hz, 1 H), 6.25 (s, 1 H), 6.75 (s, 1 H), 7.61–7.66 (m, 2 H), 7.94 (s, 2 H), 8.21–8.26 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.4, 72.3, 123.8, 123.9, 127.5, 128.9, 132.1, 140.2, 145.5, 148.0, 152.4, 162.9 ppm. ESI-MS: m/z = 372 $[M]^+$. $C_{18}H_{16}N_2O_7$ (372.33): calcd. C 58.06, H 4.33, N 7.52; found C 58.17, H 4.41, N 7.40.

(*R*)-1,1,1,3,3,3-Hexafluoroprop-2-yl 2-[Hydroxy(4-nitrophenyl)-methyl]acrylate (5g): Following the general procedure (2 mL of DMF, catalyst **2a**, –55 °C, 2 h) the title compound was obtained in 63% yield as a colourless oil. The identity was verified by comparison of its ^{1}H NMR spectra with the literature data.[5a] The *ee* of the product was determined after derivatization to the corresponding methyl ester, by HPLC using a Chiralcel OD-H column (*n*-hexane/*i*PrOH, 95:5; flow rate 0.7 mL/min; λ = 210 nm): t_R = 32.2 (*R*), 35.3 (*S*) min; 91% *ee*. $[\alpha]_D^{25}$ = –39.4 (c = 1.33, $CHCl_3$); 91% *ee*. The absolute configuration of compound **5g** was determined as (*R*) by comparison of its optical rotation with the literature value {$[\alpha]_D^{25}$ = –39.7 (c = 1.01, $CHCl_3$); 91% *ee*[5a]}.

(*R*)-2,6-Dimethyl-4-nitrophenyl 2-[(4-Chlorophenyl)(hydroxy)methyl]acrylate (5h): Following the general procedure (0.5 mL of DMF, catalyst **2a**, 0 °C, 4 d) the title compound was obtained in 53% yield as a white amorphous solid. Recrystallization from diethyl ether (3 crops) furnished the product as colourless crystals in 43% final yield; m.p. 99–103 °C. The *ee* of the product was determined by HPLC using a Chiralcel OD-H column (*n*-hexane/*i*PrOH, 97:3; flow rate 1.0 mL/min; λ = 210 nm): t_R = 44.1 (*R*), 49.3 (*S*) min; 90 and 98% *ee* before and after recrystallization, respectively]. $[\alpha]_D^{25}$ = –14.7 (c = 2.60, CH_2Cl_2); 98% *ee*. The absolute configuration of compound **5h** was assumed as (*R*) by chemical analogy with all the other cases. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.05 (s, 6 H), 2.68 (br. s, 1 H), 5.66 (s, 1 H), 6.22–6.23 (m, 1 H), 6.68 (s, 1 H), 7.31–7.40 (m, 4 H), 7.92 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.3, 72.4, 127.9, 128.2, 128.8, 132.2, 134.2, 139.5, 140.8, 145.4, 152.6, 163.0 ppm. ESI-MS: m/z = 361 $[M\ (^{35}Cl)]^+$. $C_{18}H_{16}ClNO_5$ (361.78): calcd. C 59.76, H 4.46, N 3.87; found C 59.83, H 4.52, N 3.79.

(*R*)-2,6-Dimethyl-4-nitrophenyl 3-Hydroxy-2-methylenepentanoate (5i): Following the general procedure (catalyst **2a**, –35 °C, 18 h) the title compound was obtained in 46% yield as a colourless oil. The *ee* of the product was determined by HPLC using a Chiralcel OD-H column (*n*-hexane/*i*PrOH, 95:5; flow rate 1 mL/min; λ = 210 nm): t_R = 12.1 (*R*), 13.8 (*S*) min; 99% *ee*. $[\alpha]_D^{25}$ = +0.5 (c = 1.05, $CHCl_3$); 99% *ee*. The absolute configuration of compound **5i** was determined as (*R*) after conversion into the corresponding methyl ester and comparison of its optical rotation {$[\alpha]_D^{25}$ = +7.8 (c = 0.61, $CHCl_3$); 99% *ee*} with the literature value {$[\alpha]_D$ = +7.7 (c = 0.50, $CHCl_3$), 100% *ee*[20]}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.4 Hz, 3 H), 1.69–1.86 (m, 2 H), 2.25 (s, 6 H), 2.29 (br. s, 1 H), 4.49 (q, J = 6.2 Hz, 1 H), 6.12 (s, 1 H), 6.61 (s, 1 H), 8.00 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.1, 16.8, 29.4, 72.8, 124.0, 127.7, 132.4, 141.4, 152.8, 163.6 ppm. ESI-MS: m/z = 279 $[M]^+$. $C_{14}H_{17}NO_5$ (279.29): calcd. C 60.21, H 6.14, N 5.02; found C 60.32, H 6.21, N 4.90.

(*R*)-2,6-Dimethyl-4-nitrophenyl 3-Hydroxy-4-methyl-2-methylene-pentanoate (5j): Following the general procedure (catalyst **2a**, –18 °C, 4 d) the title compound was obtained in 43% yield as a colourless oil. The *ee* of the product was determined by HPLC using a Chiralcel OD-H column (*n*-hexane/*i*PrOH, 90:10; flow rate 0.5 mL/min; λ = 210 nm): t_R = 13.5 (*R*), 16.1 (*S*) min; 95% *ee*. $[\alpha]_D^{25}$ = –5.2 (c = 2.24, $CHCl_3$); 95% *ee*. The absolute configuration of compound **5j** was determined as (*R*) after conversion into the corresponding methyl ester and comparison of its optical rotation {$[\alpha]_D^{25}$ = +12.7 (c = 0.78, $CHCl_3$); 95% *ee*} with the literature value {$[\alpha]_D^{24}$ = +13.1 (c = 0.38, $CHCl_3$); 99% *ee*[5a]}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.6 Hz, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), 1.91–2.10 (m, 1 H), 2.15 (br. s, 1 H), 2.24 (s, 6 H), 4.26 (d, J = 6.2 Hz, 1 H), 6.09 (s, 1 H), 6.63 (s, 1 H), 7.99 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.5, 17.2, 19.5, 32.8, 77.0, 123.8, 128.3, 132.3, 140.6, 145.4, 152.8, 163.4 ppm. ESI-MS: m/z = 293 $[M]^+$. $C_{15}H_{19}NO_5$ (293.32): calcd. C 61.42, H 6.53, N 4.78; found C 61.49, H 6.60, N 4.67.

Supporting Information (see footnote on the first page of this article): Computational details, cartesian coordinates, energies and number of imaginary frequencies of all the computed structures; ^{1}H and ^{13}C NMR spectra of new compounds.

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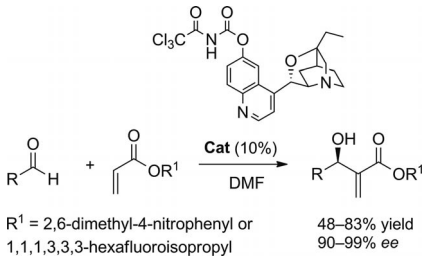
Asymmetric Catalysis

β-Isocupreidine derivatives were used to catalyze the asymmetric Morita–Baylis–Hillman (MBH) reaction, giving the (*R*)-MBH adducts in excellent optical purities and moderate to good yields. Both 2,6-dimethyl-4-nitrophenyl and hexafluoroisopropyl acrylate could be used. The rate- and selectivity-determining step was identified and the structures of the preferred transition states were computed.



Keywords: Asymmetric catalysis / Computational chemistry / Donor-acceptor systems / Enantioselectivity / Transition states

