

Construction of Adjacent Quaternary and Tertiary Stereocenters via an Organocatalytic Allylic Alkylation of Morita–Baylis–Hillman Carbonates

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Abstract: Racemic Baylis–Hillman carbonates can be converted in densely functionalized products by reaction with cyano esters in the presence of a catalytic amount of a modified *Cinchona* alkaloid in high enantioselectivities and fair diastereoselectivities. A rationale for the observed stereoselectivity is presented.

Keywords: allylic substitution; asymmetric catalysis; Baylis–Hillman reaction; *Cinchona* alkaloids; hydrogen bond

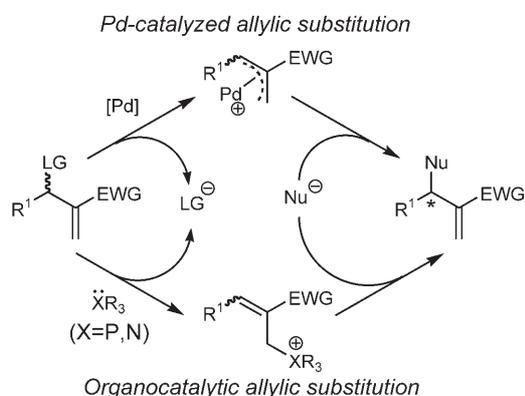
The enantioselective construction of all-carbon quaternary stereocenters still represents a major challenge in synthetic organic chemistry.^[1] The simultaneous generation of two adjacent quaternary and tertiary stereocenters is even more problematic and, to date, only few examples have been reported, all of them relying on conjugate additions.^[2]

The Morita–Baylis–Hillman (MBH) reaction has attracted the attention of many research groups, due to the possibility of accessing densely functionalized products in one step.^[3] In the last decade, these efforts have resulted in great progress being made in terms of rate, scope and enantioselectivity. Upon conversion of the alcohol to a leaving group, MBH adducts become substrates for asymmetric allylic substitution. Trost and co-workers successfully applied this strategy to the synthesis of natural products employing chiral palladium catalysts in the dynamic kinetic resolution of MBH acetates.^[4]

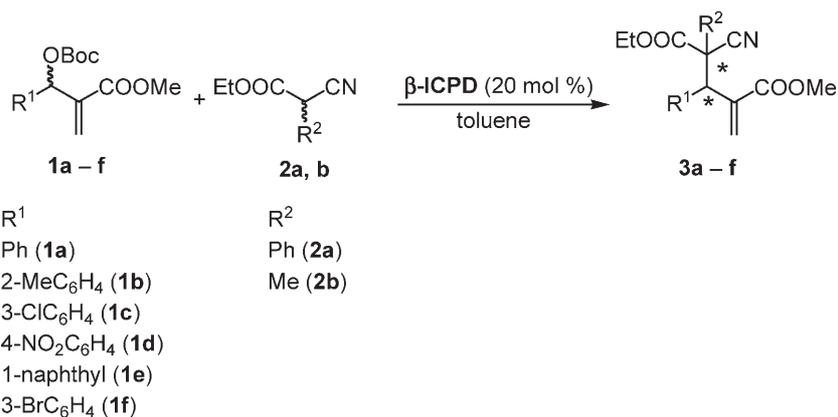
More recently, other groups investigated the feasibility of this reaction with an (asymmetric) nucleo-

philic organocatalyst,^[5] relying on a tandem S_N2'/S_N2' substitution sequence (Scheme 1).

DABCO^[6] and triphenylphosphine^[7] were shown to catalyze the allylic substitution of MBH adducts with good regioselectivity. Krische et al. reported that commercially available Cl-OMe-BIPHEP promotes the amination of MBH acetates with phthalimide in 56% *ee*.^[8] *Cinchona* derivatives were also employed as catalysts for related transformations: (DHQD)₂PHAL was used in the asymmetric hydrolysis of MBH acetates with sodium bicarbonate, giving medium to high levels of asymmetric induction (up to 84% *ee*).^[9] Lu and co-workers investigated the reaction of MBH carbonates with a variety of nucleophiles in the presence of a catalytic amount of β-isocupreidine (β-ICPD),^[10] a strained quinidine derivative that was earlier used by Hatakeyama et al. to achieve excellent levels of enantioselection in the parent MBH reaction of aldehydes and activated acrylates.^[11] Remarkably, besides



Scheme 1. Organocatalytic vs. Pd-catalyzed allylic substitution.

Table 1. Substrate scope for the organocatalytic allylic alkylation.^[a]

Entry	Product	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[b]	<i>dr</i> ^[c]	<i>ee</i> [%] ^[d]
1		−20	48	94	4:1	83
2		0	96	95	4:1	79
3		−20	72	95	1.4:1	80
4		−20	48	95	1.1:1	16
5		20	24	66 ^[e]	4:1	85
6		−20	72	95 ^[f]	3:1	80

^[a] Reaction conditions: 0.6 mmol **1**, 0.3 mmol **2**, 0.06 mmol β -ICPD in 6 mL toluene.

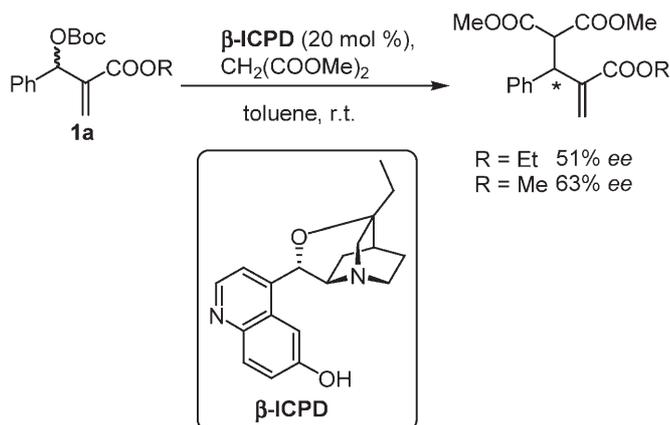
^[b] Isolated yield (mixture of diastereomers).

^[c] Determined by ¹H NMR analysis of the crude reaction mixture.

^[d] The *ee* value of the major diastereoisomer was determined by chiral HPLC.

^[e] Compound **3e** was obtained as a pure diastereomer.

^[f] Reaction performed on 9.0 mmol of **1f**



Scheme 2. Reaction of an MBH carbonate with dimethyl malonate.

nitrogen and oxygen nucleophiles, the authors reported the reaction of an MBH carbonate with dimethyl malonate. Although the enantioselectivity was moderate (51% *ee*), Lu and co-workers established for the first time the possibility of using carbon nucleophiles for an organocatalytic allylic alkylation. In this communication we report our investigations on the same reaction using prochiral tertiary nucleophiles thus leading to products with two adjacent quaternary/tertiary stereocenters.

In our preliminary experiments, we re-investigated the reaction of carbonate **1a** with dimethyl malonate in the presence of β -ICPD: although screening of different reaction conditions (solvent, concentration, temperature) did not improve the results reported by Lu, we found that the employment of a methyl ester as the electrophile resulted in slightly higher levels of asymmetric induction (63 vs. 51% *ee*, Scheme 2).

Next, we examined the reaction of compound **1a** with highly reactive ethyl α,α -cyanophenylacetate (**2a**) in toluene at room temperature. The reaction went to completion in less than 24 h with high regioselectivity yet moderate stereoselectivity (*dr* 3:1, 68% *ee* for the major diastereomer). Employment of an excess of compound **1a** gave a strong rate enhancement, probably due to a kinetic resolution effect (see later), allowing the reaction to be carried out at a lower temperature. Gratifyingly, performing the reaction at -20°C with 20 mol % of β -ICPD resulted in full conversion to the adduct **3a** in 83% *ee* (*dr* 4:1). We then examined different combinations of reaction partners (Table 1). In general, compounds **3** were obtained in high yields and good enantioselectivities. Substrate **1d** gave disappointing results, possibly due to its high reactivity towards conjugate addition. Hindered substrates (**1b** and **1e**, entries 2 and 5) required slightly higher temperatures to obtain satisfying reaction rates; fortunately, the level of enantioselection was not negatively affected.

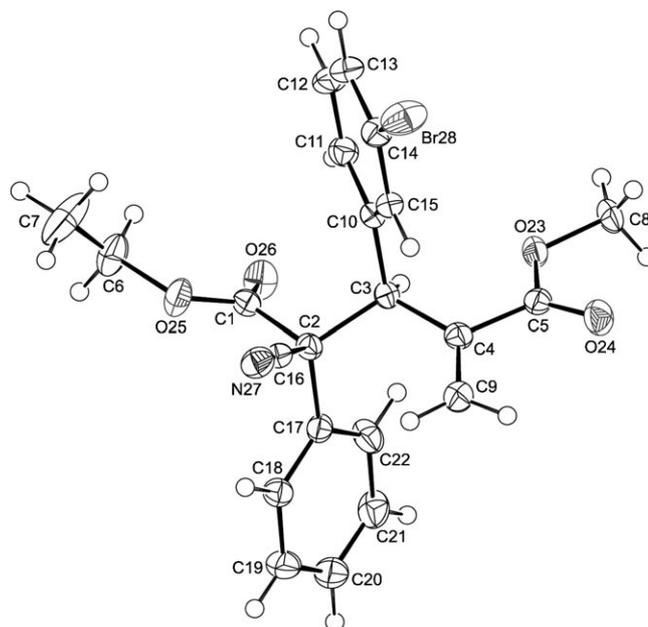
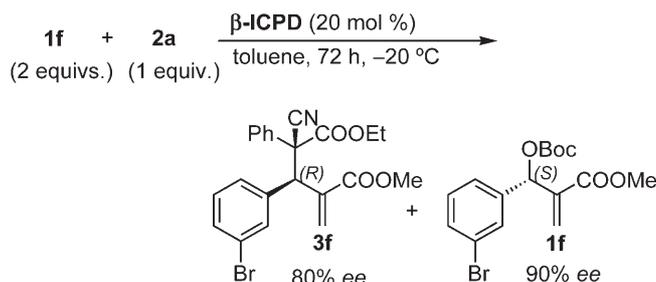


Figure 1. Displacement ellipsoid plot of compound **3f** in the crystal, drawn at the 50% probability level.



Scheme 3. Kinetic resolution of MBH carbonate **1f**.

As some adducts were obtained as crystalline solids after chromatography, we ran a reaction on a gram scale with the aim to upgrade the optical purity of the product *via* recrystallization. Hence, compound **1f** (3.3 g, 9.0 mmol) was reacted with cyanoacetate **2a** (0.78 mL, 4.5 mmol) to afford, after chromatography, adduct **3f** in 80% *ee* and 95% yield (entry 7). A single recrystallization from cyclohexane afforded compound **3f** (59% yield, calculated on cyanoacetate **2a**) with 98% *ee* as a pure diastereomer.^[12] X-ray analysis of these crystals allowed an unambiguous assignment of the absolute and relative configuration (Figure 1).^[13]

Interestingly, HPLC analysis of the recovered starting material (**1f**) gave evidence for a kinetic resolution effect (Scheme 3). Compound **1f** was isolated from the crude mixture after column chromatography in 90% *ee*. Recrystallization afforded enantiopure crystals (47% yield based on **2a**) whose absolute con-

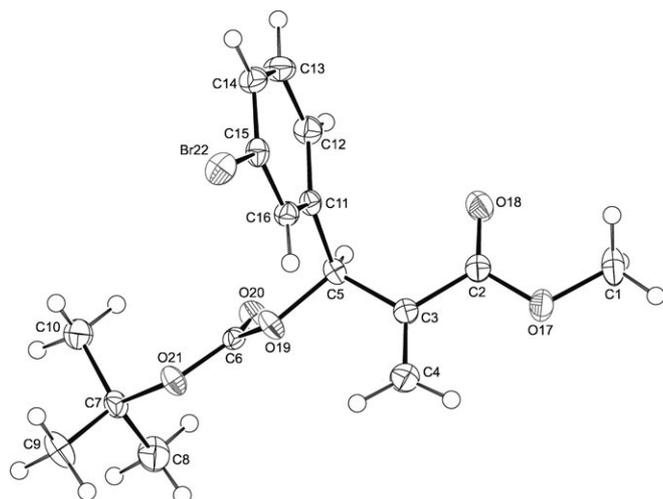


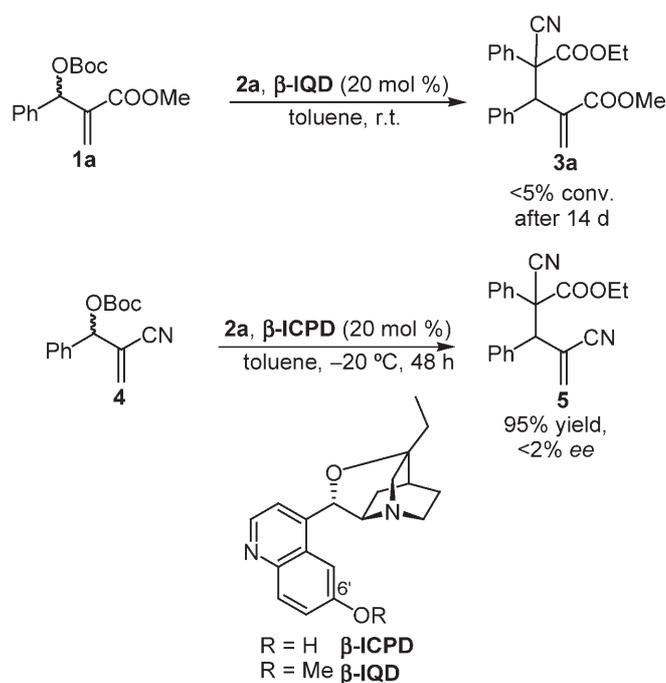
Figure 2. Displacement ellipsoid plot of compound **1f** in the crystal, drawn at the 50% probability level.

figuration could be determined with X-ray spectroscopy (Figure 2).

As suggested by Kim and co-workers,^[9] who observed a similar effect, this can be explained in terms of a kinetic resolution in the first step. This process, however, does not affect the stereoselectivity of the second conjugate addition generating the C–C bond. To confirm that we examined the reaction of 1 equivalent of **1a** with 2 equivalents of **2a** at room temperature (hence reversing the reagents ratio): after 24 h, **1a** was completely converted to **3a** with similar stereoselectivity (68% *ee*, 3:1 *dr*), showing that both enantiomers of the MBH carbonate undergo Michael addition although with different rates, followed by elimination of the leaving group leading to the same intermediate.

Next, we investigated the role of the C-6'-OH of β -ICPD, which was shown to be fundamental in the Baylis–Hillman reaction.^[11] When β -isoquinidine (β -IQD) was used as the catalyst, less than 5% conversion was observed after two weeks. Furthermore, substrate **4**, featuring a cyano group (a poorer hydrogen bond acceptor) instead of a methyl ester, underwent allylic substitution giving adduct **5** in high yield but no asymmetric induction was observed (Scheme 4).

On the basis of all these observations, we propose a tentative hypothesis to rationalize our experimental results (Scheme 5). First, substrate **1a** undergoes a conjugate addition to form adduct **A**. Subsequently, elimination of the OBoc group, leading to the formation of CO₂ and *tert*-butoxide anion provides Michael acceptor **B**. We believe that this irreversible reaction step is responsible for the observed kinetic resolution. As shown in the experiment with β -isoquinidine, the presence of the C-6'-OH in the catalyst is required for activation of the ester prior to conjugate addition. As already proposed by Lu,^[10] the *tert*-butoxide anion de-



Scheme 4. Effects of the structure of catalyst and substrate.

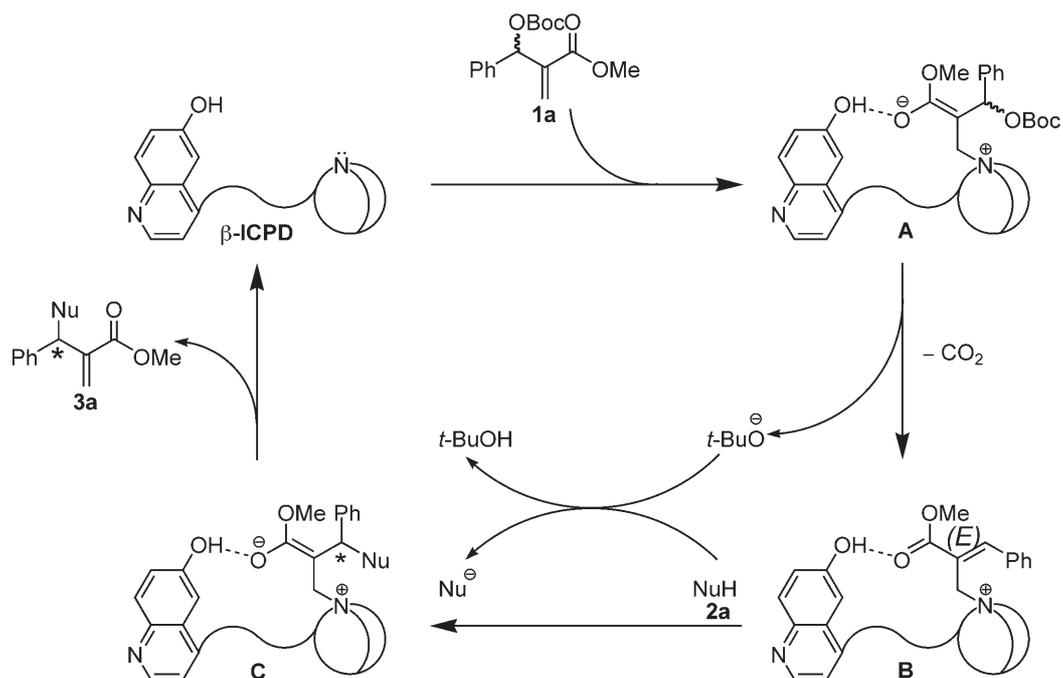
protonates cyanoacetate **2a** which, in turn, attacks the α,β -unsaturated intermediate **B**, present as the *E* isomer, as previously shown by Kim and co-workers.^[9] Probably, an intramolecular hydrogen bond between the phenolic OH and the ester moiety is responsible for the face shielding conferring stereoselectivity to the reaction; a DFT-minimized structure of **B** supporting this hypothesis is depicted in Figure 3. Elimination of the catalyst from intermediate **C** liberates alkylated product **3a**, closing the catalytic cycle.

In conclusion, we have developed a new methodology to access highly functionalized compounds featuring two adjacent stereocenters, one of them bearing four carbon substituents. We also demonstrated for one example that the same reaction can be exploited as a kinetic resolution to obtain highly enantioenriched MBH carbonates.

Experimental Section

General Procedure for the Asymmetric Allylic Alkylation of MBH Carbonates (**1a–f** and **4**)

β -ICPD (20 mol%) was added to the total volume of toluene and the resulting suspension was heated and stirred until formation of a clear solution. Subsequently, the mixture was allowed to cool to the indicated temperature. The MBH carbonate (**1a–f** or **4**) was added to the reaction mixture and the mixture was stirred until complete dissolution (~5–10 min). Cyanoacetate (**2a** or **b**) was added in one portion and the mixture was kept at the indicated temperature for the described reaction time. The experiments were stop-



Scheme 5. Proposed mechanism.

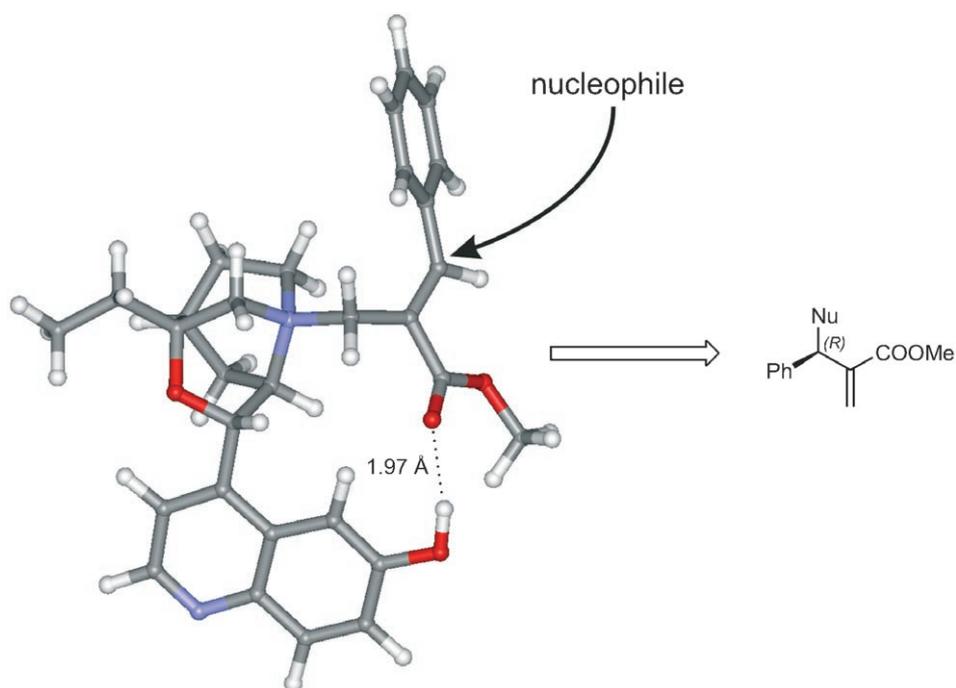


Figure 3. Minimized structure of intermediate B (B3LYP/6-31G**).

ped by filtration of the reaction mixture over a short pad of silica gel and elution with Et_2O . Solvents were removed by rotary evaporation and the crude mixture was purified by column chromatography.

Acknowledgements

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- [12] Similar results were obtained with carbonate **1a**: adduct **3a** was obtained as a single diastereomer in 63% yield and 99% *ee* after recrystallization; see Supporting Information for details.
- [13] Experimental details of the crystal structure determinations for **3f**, **1f**, and **3a** are given in the Supporting Information. CCDC-619143 (compound **3f**), CCDC-619144 (**1f**) and CCDC-619145 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.