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Enantioselective organocatalytic asymmetric allylic alkylation. Bis(phenylsulfonyl)methane addition to MBH carbonates†

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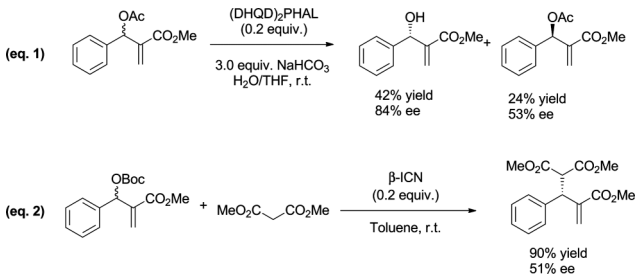
The highly enantioselective asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates with bis(phenylsulfonyl)methane is presented. The reaction is simply catalyzed by cinchona alkaloid derivatives affording the final alkylated products in good yields and enantioselectivities.

In recent years, one of the major goals for organic chemists has been the synthesis of asymmetric C–C bonds. Allylic substitution has emerged as one of the most powerful methods for the enantioselective synthesis of C–C bonds.[1]

In 1977, Trost and co-workers reported the first example of an enantioselective catalyzed allylic substitution with a stabilized nucleophile.[2] Since then, much study has been carried out on the asymmetric potential of allylic alkylations. One of the outcomes of this research was the development of new methods based on transition metal catalysts; these methods turned asymmetric allylic alkylation (AAA) into a powerful tool for the synthesis of asymmetric C–C bonds. Most of these methods use Pd as the metal catalyst, but transition metals complexes of Ir, Rh, or Cu have also been used to give excellent results. Despite these successes, it was not until 2002 that the organocatalytic version of this important reaction was developed by Kim and co-workers, who reported the use of cinchona alkaloid derivatives for the hydrolysis of Morita–Baylis–Hillman (MBH) acetates with sodium bicarbonate.[3] (Scheme 1, eq. 1) Since then, the allylic alkylation of MBH adducts catalyzed by a metal-free organic Lewis-base has attracted considerable attention from the organic chemistry community.

Following the pioneering report of Kim, Krische reported in 2004, that Cl-OMe-BIPHEP promotes the amination of MBH acetates with phthalimides.[4] In the same year, the first dynamic kinetic resolution of MBH carbonates using different nucleophiles was developed by Lu and coworkers.[5] Remarkably, in this work, the authors reported the reaction of an MBH carbonate with dimethyl malonate. Despite the low enantioselectivity of the reaction, Lu and co-workers established for the first time, the possibility of using carbon nucleophiles for an organocatalytic allylic alkylation (Scheme 1, eq. 2).



Scheme 1 Pioneering works with MBH derivatives.

Two years later, Hiemstra and co-workers reported the synthesis of adjacent quaternary and tertiary stereocenters *via* the organocatalytic allylic alkylation of MBH carbonates using β-isocupreidine as catalyst.[6] Since these initials reports, several research groups have developed similar reactions for synthesizing the C–C bond. For example, Y.-C. Chen and co-workers reported the use of α,α-dicyanoalkenes as a suitable nucleophile for this reaction, affording the final allylic derivatives in excellent yields and enantioselectivities.[7] Soon after, the same research group reported the alkylation of oxindoles[8] and the allylic alkylation of MBH carbonates catalyzed by cinchona alkaloid derivatives with very good results.[9]

However, in all these methods, the added fragment contains new functional groups. As a result, none of these methods is suitable for adding simple aliphatic chains.

In recent years, our research group has developed several methods for the formal alkylation of enals[10] and oxazolones[11] using bis(phenylsulfone) derivatives as the synthetic equivalent of an alkyl group, as disulfone moieties can be easily removed (Scheme 2).[12]

Based on previous reports and our experience with organocatalysis,[13] we formulated an easy entry to chiral allyl methyl derivatives *via* the nucleophilic addition of bis(phenylsulfonyl) methane to MBH carbonates.

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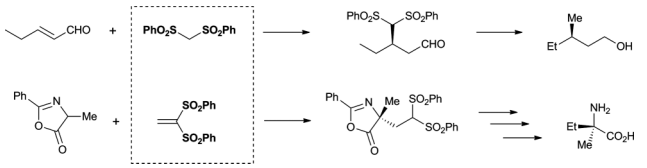
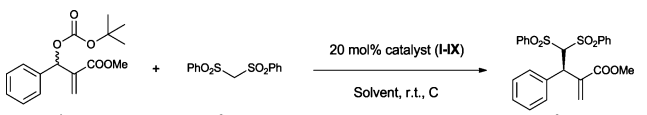


Scheme 2 Use of sulfones as alkyl equivalent developed in our research group.

In our preliminary experiments, we investigated the reaction of MBH carbonate **1a** with bis(phenylsulfonyl)methane **2a** in the presence of different organic chiral Brønsted bases. As it is depicted in Table 1, β-isocupreidine (β-ICPD, entry 1; Table 1) was the most active catalyst, causing full conversion of the expected product in 14 h but with low enantioselectivity. Cinchona or quinine, did not give better results in terms of yield or enantioselectivity (entries 2–3; Table 1). On the opposite hand, Sharpless ligands catalyze the reaction smoothly but with higher enantioselectivities (entries 6–9; Table 1). Dichloromethane, MTBE, AcOEt or MeOH are suitable solvents to run the reaction in, but afford the final compound in lower conversions and/or lower enantioselectivities. Finally, increasing the concentration of the reactant **1a** to 0.5 M, using $(DHQD)_2AQN$ as the catalyst in toluene at room temperature resulted in the best conditions, affording **3a** in a 57% conversion and 94% ee after 14 h (entry 16, Table 1). Further screening of different solvents or additives did not improve the results (see ESI†).

Once we determined the optimum conditions, we proceeded to study the scope of the reaction in terms of MBH carbonate. The reaction under the optimized conditions afforded the final allylic compounds in high to excellent yields and enantioselectivities. The reaction was found to tolerate halogen atoms on the aromatic moiety, including 2-Br or 4-F, affording the final compounds in 83% and 94% yield and 91% and 94% enantioselective excess, respectively (entries 2 and 3; Table 2). When an electron donating group (4-MeO) was present on the aromatic moiety, the reaction produced the compound **3d** with 89% yield and the enantioselectivity increased to 99% (entry 4; Table 2). The use of naphthyl derivatives afforded the final products with excellent yields and enantioselectivities. In particular, when 1-naphthyl derivatives were used, the reaction produced an almost enantiopure final product (entry 5; Table 2). The reaction tolerated different substituents on the aryl ring, including Cl, CN, and even CF_3, without any decrease in the yields or enantioselectivities (entries 7–9; Table 2). We also studied the use of different ester substituents in order to examine the effect of the bulkiness of the ester moiety in terms of yield and stereoselectivity. As shown in Table 2, entries 10 and 11, when the steric hindrance of the ester moiety increases, a slight decrease in enantioselectivity is observed. Surprisingly, when cyclic 1,3-benzodithiole-1,1,3,3-tetraoxide **2b**,

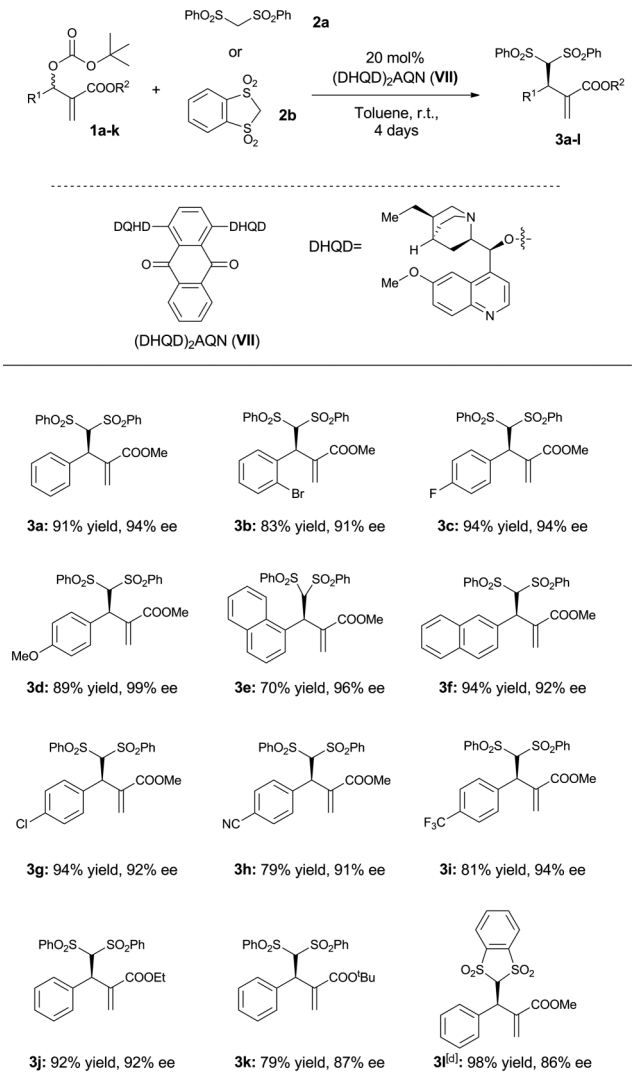
Table 1 Conditions screening[a]



Entry	Catalyst	Solvent	Conc.	Conv. (14 h)[b]	ee[c]
1	β-ICPD (**I**)	Toluene	0.1 M	100%	26%
2	Quinine (**II**)	Toluene	0.1 M	70%	13%
3	Cinchonine (**II**)	Toluene	0.1 M	traces	n.d.
4	$(DHQD)_2PHAL$ (**IV**)	Toluene	0.1 M	20%	64%
5	$(DHQ)_2PHAL$ (**V**)	Toluene	0.1 M	15%	−65%
6	$(DHQD)_2AQN$ (**VI**)	Toluene	0.1 M	36%	95%
7	$(DHQ)_2AQN$ (**VII**)	Toluene	0.1 M	33%	−48%
8	$(DHQD)_2PYR$ (**VIII**)	Toluene	0.1 M	63%	94%
9	$(DHQD)_2PYR$ (**IX**)	Toluene	0.1 M	5%	−81%
10	$(DHQD)_2AQN$ (**VI**)	CH_2Cl_2	0.1 M	56%	86%
11	$(DHQD)_2AQN$ (**VI**)	MeOH	0.1 M	10%	97%
12	$(DHQD)_2AQN$ (**VI**)	TBME	0.1 M	13%	98%
13	$(DHQD)_2AQN$ (**VI**)	AcOEt	0.1 M	79%	94%
14	$(DHQD)_2AQN$ (**VI**)	DMF	0.1 M	16%	70%
15	$(DHQD)_2AQN$ (**VI**)	Toluene	0.25 M	37%	94%
16	$(DHQD)_2AQN$ (**VI**)	Toluene	0.5 M	57%	94%

[a] In a small flask, **1a** (1.2 equiv), **2a** (1 equiv.) and catalyst (10 mol%) were added in 0.5 mL toluene. [b] Determined by ^1H NMR of the crude reaction. [c] Determined by chiral HPLC

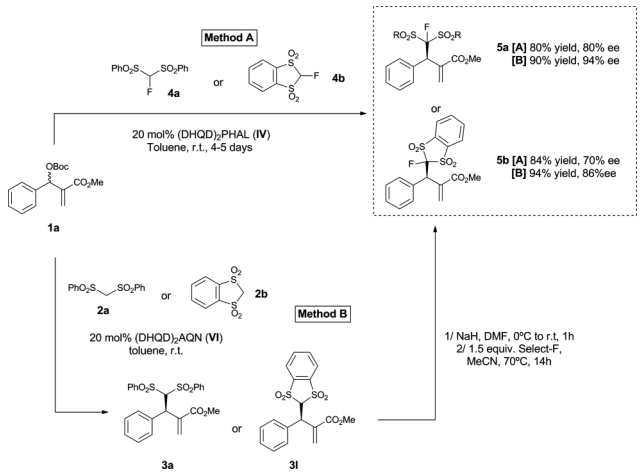
Table 2 Scope of the reaction[a,b,c]



[a] In a small flask, **1a–k** (1.2 equiv), **2a** (1 equiv.) and $(DHQD)_2AQN$ (10 mol%) were added in 0.5 mL toluene. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Using sulfone **2b** as nucleophile.

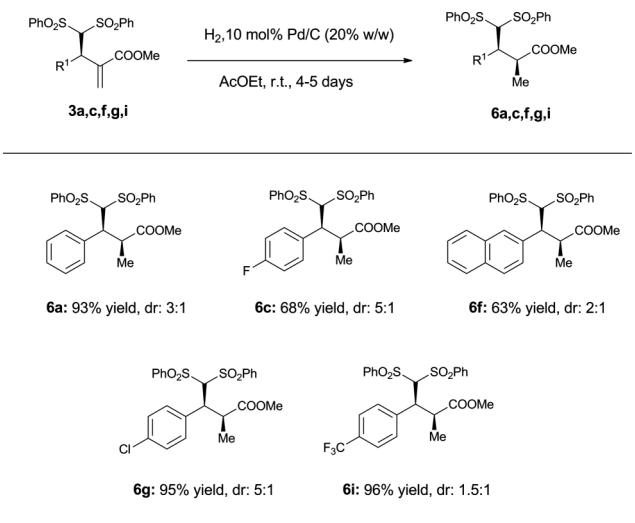
which was previously reported by Palomo and co-workers,[10d] is used, the reaction produces the final product in higher yields and lower enantioselectivities (entry12; Table 2).

To perform the synthesis of fluoro methyl derivatives, we studied the addition of fluoromethylenebissulfone derivatives to the MBH carbonates. Unfortunately, the addition of fluoromethylenebissulfones **4a** and **4b**[15] requires long reaction times and produces the desired fluoro derivatives in lower yields and enantioselectivities than the previously reported methylenbissulfones. Therefore, a suitable synthetic pathway for the synthesis of fluoro derivatives would probably require two simple steps, first addition of bis(phenylsulfonyl)methane to the MBH carbonate and subsequently fluorination (Scheme 3).



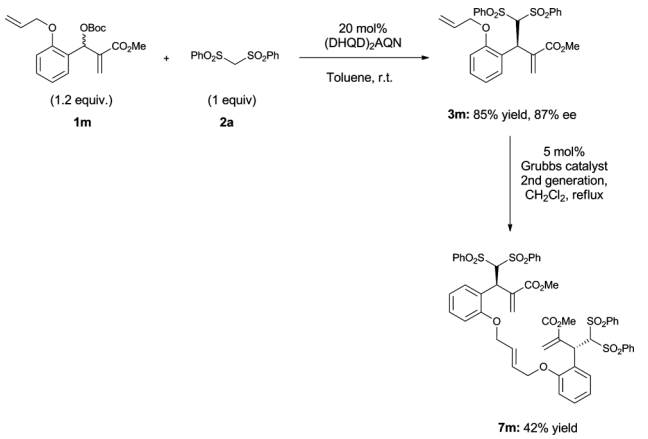
Scheme 3 Synthesis of fluoromethyl derivatives.

Next, we decided to study the applicability of the reaction by derivatization of compounds **3**. The reduction of the double bond was achieved by treatment of compounds **3** with Pd over H_2, affording the hydrogenated compounds in excellent yields and moderate to good diastereoselectivities (Scheme 4).



Scheme 4 Hydrogenation of compounds **3**.

Moreover, we have shown the applicability of this reaction to the synthesis of highly complex structures like **7m** by simple cross metathesis in good yields (Scheme 5).



Scheme 5 Derivatization of compound **3m**.

The absolute configuration of compound **3a** was ascertained by a single crystal X-ray analysis (Fig. 1).[14] The X-ray crystal structure unambiguously shows that the enantiomer obtained from the $(DHQD)_2AQN$ has the (*R*) configuration.

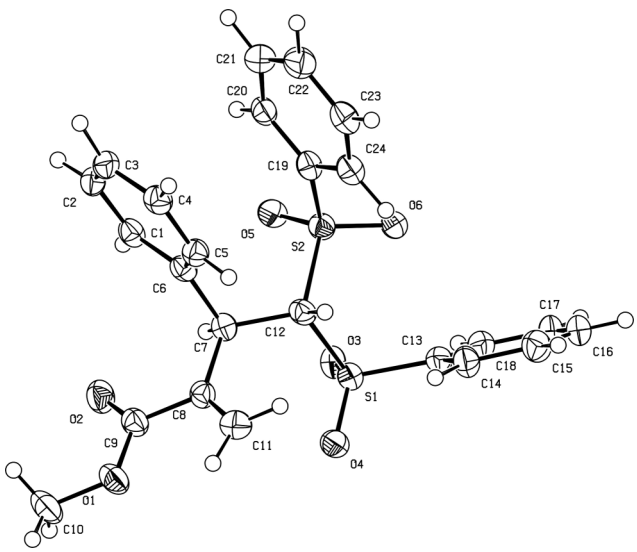


Fig. 1 ORTEP diagram for **3a**.

To understand the mechanism of the reaction, we performed several experiments to study the behavior of the starting materials and the products during the reaction. We checked the enantioselectivity of the starting material and the final products at different stages to understand a plausible mechanism pathway. As shown in Fig. 2, the enantioselectivity of the final compound is independent of the reaction conversion. This data indicates a common diastereopure intermediate in the reaction. However, the starting material increased the enantiopurity with conversion. This behavior indicates a kinetic resolution of the MBH-carbonate

With this information we suggest the mechanism illustrated in Scheme 6. First substrate **1a** undergoes a conjugate addition, followed by elimination of the OBoc group leading to the formation of CO_2 and *tert*-butoxide anion, which provides Michael acceptor A. This step is responsible for the observed kinetic resolution of the MBH carbonates. Next, the nucleophile attacks from Re face (the Si face of the MBH adduct is blocked by the catalyst) the intermediate B to afford the final product.

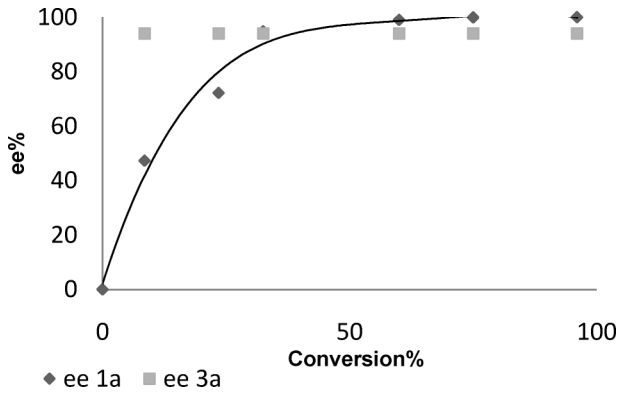
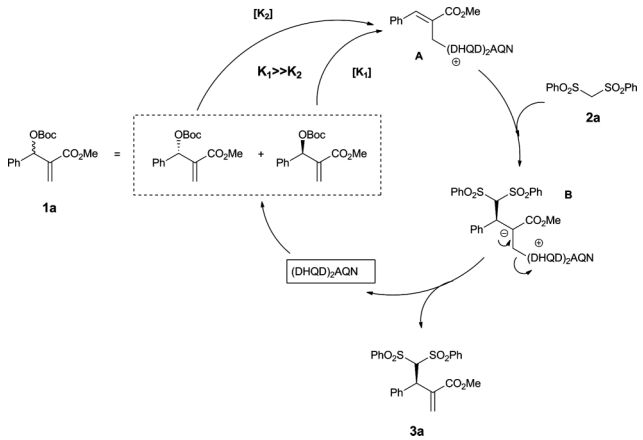
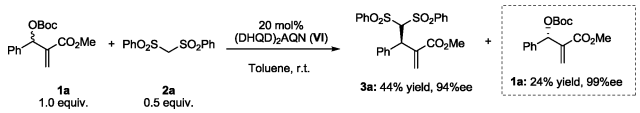


Fig. 2 Kinetic resolution of **1a**.[16]



Scheme 6 Proposed S_N2'-S_N2' mechanism.

Moreover, we conducted a reaction using only 0.5 equivalents of **2a**, affording after column chromatography the unreacted starting material in 24% yield and 99% ee (Scheme 7).[17]



Scheme 7 Kinetic resolution of BOC carbonates.

Conclusions

To summarize, we have described a practical, inexpensive, and powerful method as an organocatalytic alternative for organometallic allylic substitution. We have achieved an asymmetric bis(phenylsulfonyl)methane addition to MBH carbonates with excellent yields and enantioselectivities. Moreover, we showed the broad applicability of this method not only for synthesizing derivatives but also for removing the bis sulfone moiety to give access to a formal allylic methylation.[18]

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