# Bis(2-aminobenzoimidazole)-Organocatalyzed Asymmetric Alkylation of Activated Methylene Compounds with Benzylic and Allylic Alcohols

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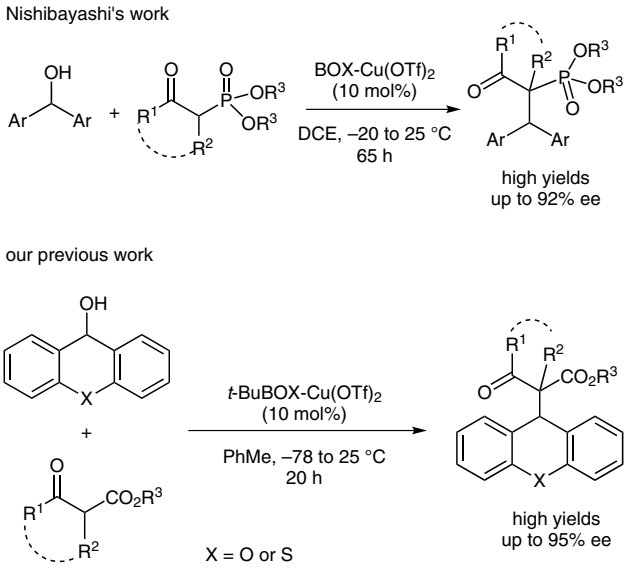
**Abstract:** The first organocatalyzed asymmetric alkylation of activated methylene compounds using benzylic and allylic alcohols as alkylating agents through dual hydrogen bond activation in an $S_N1$-type reaction is reported. This green protocol employs a bis(2-aminobenzoimidazole) in combination with an achiral Brønsted acid as a bifunctional catalytic system and gives the alkylation products with moderate to good enantioselectivities. Although the scope of the reaction is limited, this methodology can be considered as complementary to existing metal-catalyzed processes. In addition, modest results were obtained in a first attempt to perform a metal-free asymmetric Tsuji–Trost reaction using allylic alcohols. Finally, the recovery and reusability of the organocatalyst is also achieved.

**Key words:** asymmetric catalysis, alcohols, organocatalysis, carbocations, alkylation

The asymmetric alkylation of prochiral carbon nucleophiles using benzylic alcohols as alkylating agents, through an $S_N1$-type reaction, has emerged over the last few years an environmentally friendly alternative route to the previously reported and well-established methodologies for enantioselective C–C bond formation, since this process has perfect atom-economy and only generates water as a by-product.[1] However, the prochiral carbon nucleophiles that have been used to date seem to be limited to the use of aldehydes. Since the pioneer work by Cozzy and co-workers, on the organocatalyzed asymmetric α-alkylation of aldehydes using such alcohols through an enamine activation mode,[2] several examples have recently appeared, the majority following a similar strategy.[3]

Despite the versatility of activated methylene compounds, such as dicarbonyl compounds, β-keto esters, α-cyanoacetates, α-nitroacetates, β-keto sulfones, etc., as building blocks which are easily transformed into other functionalities and the multiple strategies reported for their activation employing chiral catalysts,[4] reported methodologies for their use as prochiral nucleophiles in asymmetric alkylations with benzylic alcohols remain rare. To the best of our knowledge, there are only two reports in this regard recently reported by Nishibayashi and our group, disclosing the asymmetric alkylation of β-keto phosphonates[5] and β-keto esters[6] respectively, catalyzed by BOX–$Cu(OTf)_2$-type complexes (Scheme 1).




**Scheme 1** Previous asymmetric alkylations of active methylene compounds with benzylic alcohols

Continuing with this research[7] and based on the experience of our group in organocatalyzed asymmetric reactions involving activated methylene compounds in Michael-type additions,[8] we envisaged a possible metal-free strategy through dual hydrogen bond activation (Figure 1) that would represent the first organocatalyzed version of this transformation. The results of this study are presented herein.

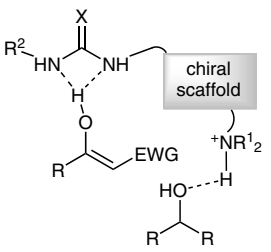



**Figure 1** Hypothetic dual hydrogen bond activation working model

Firstly, in the search for optimal reaction conditions we selected the reaction between bis[4-(dimethylamino)phenyl]methanol (**1a**), which would produce a rather stable carbocationic intermediate ($E = -7.02$)[9] and ethyl 2-oxocyclopentanecarboxylate (**2a**) as model reaction (Table 1). This particular reaction failed completely in our previ-

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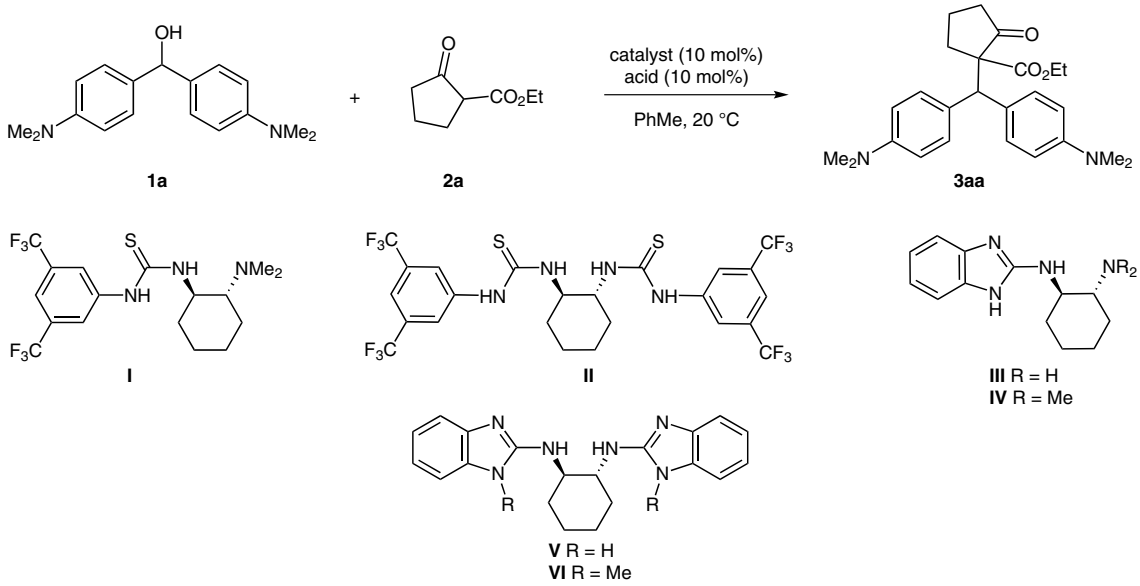
ous work when using *t*-Bu-BOX–copper(II) catalyst.[6] Thus, different catalysts derived from *trans*-cyclohexane-1,2-diamine **I**–**VI** (10 mol%) were studied in the presence of trifluoroacetic acid (10 mol%) as co-catalyst, which would allow the possible activation of the hydroxy group according to our hypothesized working model (Figure 1) using toluene as solvent and at 25 °C (Table 1). As observed, full conversion was achieved in all cases, but moderate enantioselection was only observed when using bis(2-aminobenzoimidazole) derivative **V**, which has already shown its effectiveness for the conjugated addition of 1,3-dicarbonyl compounds to maleimides[8e,f] (entries 1–6). Therefore, this catalyst was selected to further refine the reaction conditions. It is important to note that in the absence of acidic co-catalyst, the reaction only produced poor results at best.

Next a wide range of solvents with different properties was tested at 0 °C under the same reaction conditions, but none of them increased the results obtained with toluene (53% ee, Table 1, entry 7).[10] At this temperature several

**Table 1** Optimization of the Reaction Conditions[a]




| Entry | Catalyst | Acid | Temp (°C) | Conv.[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **I** | TFA | 25 | >95 | *rac* |
| 2 | **II** | TFA | 25 | >95 | 5 |
| 3 | **III** | TFA | 25 | >95 | *rac* |
| 4 | **IV** | TFA | 25 | >95 | 2 |
| 5 | **V** | TFA | 25 | >95 | 33 |
| 6 | **VI** | TFA | 25 | >95 | 8 |
| 7 | **V** | TFA | 0 | >95 | 53 |
| 8 | **V** | $PhCO_2H$ | 0 | 15 | 32 |
| 9 | **V** | TsOH | 0 | 25 | 50 |
| 10 | **V** | TfOH | 0 | >95 | 52 |
| 11 | **V** | TFA | –20 | 85 | 64 |
| 12 | **V** | TfOH | –20 | 90 | 67 |
| 13 | **V**[d] | TFA[d] | –20 | 50 | 67 |
| 14 | **V**[d] | TfOH[d] | –20 | 58 | 67 |

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.23 mmol), catalyst **I**–**VI** (10 mol%), acid (10 mol%), toluene (1.0 mL).
[b] Determined by $^1$H NMR analysis on the crude product.
[c] Determined by HPLC using chiral columns Daicel Chiralpak IA (see Supporting Information for details).
[d] The reaction was carried out using 5 mol% of **V** and acid.

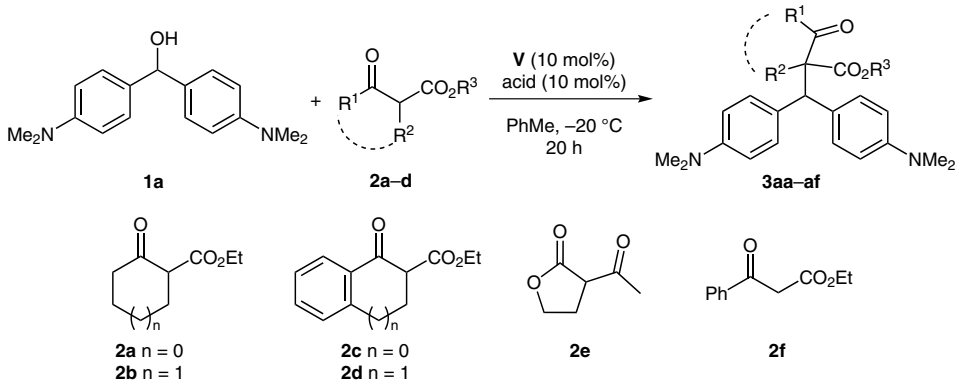
 

Brønsted acids, aside from trifluoroacetic acid, were also evaluated (entries 8–10). As result of this study, it was observed that trifluoromethanesulfonic acid behaved similarly to trifluoroacetic acid (entries 7 and 10). However, benzoic acid and 4-toluenesulfonic acid gave inferior results (entries 8 and 9). It is important to note that chiral Brønsted acids (a Binol-phosphoric acid derivative and CSA) were also tested, but unfortunately no synergistic effect was observed. Moreover, with the use of 20 mol% of acid, the enantioselectivity decreased dramatically. Finally, with the two acid co-catalysts in hand, we tried to increase the enantioselectivity of the process by lowering the temperature. Thus, at –20 °C the enantioselectivity of **3aa** increased to 64% and 67% ee when using trifluoroacetic acid and trifluoromethanesulfonic acid, respectively, as co-catalysts (entries 11 and 12). At this point, we decided to reduce the amount of catalyst to 5 mol%, in this case only moderate conversions were observed but the enantioselectivity remained approximately the same in both cases (entries 13 and 14).

In addition, the use of dry reaction conditions (by performing the reaction under and argon atmosphere and using dry solvents) or other changes in the concentration and amount of reactants did not produce any improvement in the results.

Once the optimal reaction conditions were established, 10 mol% catalyst **V**, 10 mol% trifluoroacetic acid or trifluoromethanesulfonic acid as co-catalyst, toluene, –20 °C, we decided firstly to examine the use of other β-keto esters using alcohol **1a** as the alkylating agent (Table 2). As previously mentioned, the alkylation of keto ester **2a** proceeded in high yields and good enantioselectivities under these reaction conditions with either acid co-catalyst (entries 1 and 2). It is important to note that the optical purity of **3aa** further increased to 82% ee by crystallization in hexanes (entry 2). Next, the six-membered β-keto ester **2b** was tested, and we were pleased to observe high yields and enantioselectivities when the reaction was performed at 0 °C using trifluoroacetic acid (entry 3). In contrast, the reaction failed when trifluoromethanesulfonic acid was the co-catalyst regardless the temperature employed (entry 4). The corresponding benzocondensed analogues **2c** and **2d** were also evaluated, but unfortunately the reaction was unsuccessful or if it did proceed then racemic mixtures were obtained. High yields, although with low enantioselectivities, were obtained when using lactone **2e** as

**Table 2** Asymmetric Alkylation of β-Keto Esters with **1a**[a]




| Entry | Acid | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | TFA | **3aa** | 85 | 64 |
| 2 | TfOH | **3aa** | 90 (76)[d] | 67 (82)[d] |
| 3 | TFA[e] | **3ab** | 70 | 90 |
| 4 | TfOH | **3ab** | 10 | *rac* |
| 5 | TFA | **3ae** | 77 | 16 |
| 6 | TfOH | **3ae** | 81 | 26 |
| 7 | TFA | **3af** | 70 | 38 |
| 8 | TfOH | **3af** | 40 | 37 |

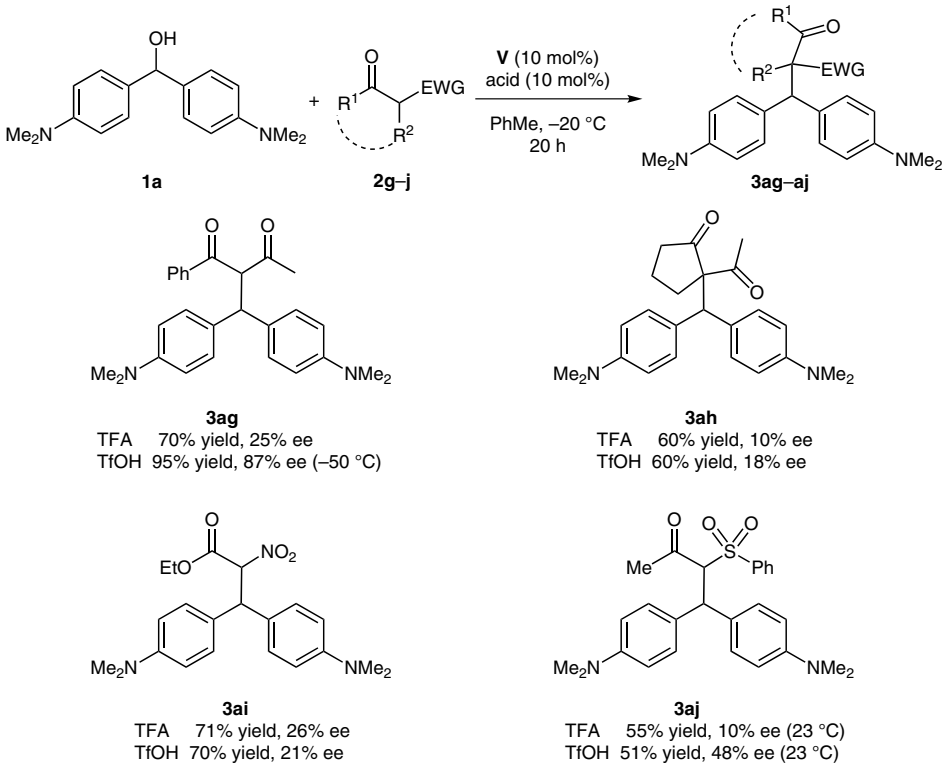
[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.23 mmol, 1.5 equiv), catalyst **V** (10 mol%), acid (10 mol%), toluene (1.0 mL), –20 °C, unless otherwise stated.
[b] Isolated yield after preparative TLC.
[c] Determined by HPLC using chiral columns Daicel Chiralpak IA (see Supporting Information for details).
[d] Yield and ee after crystallization (hexanes).
[e] The reaction was performed at 0 °C.

substrate in both cases (entries 5 and 6). Finally, several linear β-keto esters were also examined, but among these **2f** was the only success, producing **3af** with modest enantioselectivity and trifluoroacetic acid gave the best yield (entries 7 and 8). This last particular case allowed us to assume an *S*-configuration for the new created stereogenic center by comparison with our previous work.[6]

Next, the scope of the reaction towards the use of other prochiral activated methylene compounds was studied. Thus, different 1,3-diketones, α-cyanoacetates, β-keto phosphonates, α-nitroacetates, and β-keto sulfones were tested using alcohol **1a** as substrate (Scheme 2). As observed, benzoylacetone (**2g**) afforded the corresponding product **3ag** in good yield and with 87% ee when trifluoromethanesulfonic acid was the acid co-catalyst and the reaction was carried out at –50 °C. Encouraged by this result several diketones were tested, but disappointingly only low enantioselectivity was obtained at best when the five-membered diketone **2h** was employed. As mentioned, α-cyanoacetates and β-keto phosphonates were also evaluated, but no enantioselection was observed. The alkylation product **3ai** was obtained in good yield, but low enantioselectivity, when either acid was used as co-catalyst with ethyl nitroacetate (**2i**). Finally, β-keto sulfone **2j** gave the corresponding product **3aj** in moderate yield and enantioselectivity when the reaction was performed at room temperature using trifluoromethanesulfonic acid as co-catalyst.

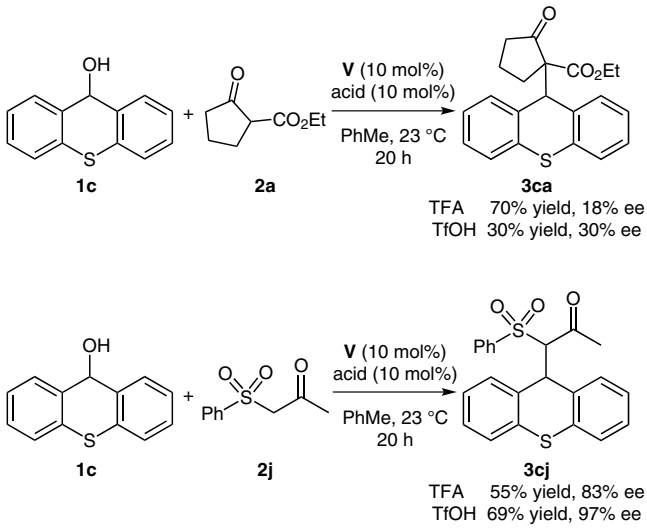
In order to extend this methodology to other benzylic alcohols we thought to use xanthenols and bis(4-methoxyphenyl)methanol (**1d**), which had already turned out to be excellent alkylating agents in the copper-catalyzed asymmetric version.[5,6] Thus, 9*H*-xanthen-9-ol (**1b**) and 9*H*-thioxanthen-9-ol (**1c**) along with **1d** were allowed to react with activated methylene compounds **2a**–**j** under the optimal reaction conditions. However, despite the good yields obtained in the majority of cases, only the reaction between 9*H*-thioxanthen-9-ol (**1c**) and keto ester **2a** and β-keto sulfone **2j** at room temperature proceeded in an enantioselective manner. In the first case, trifluoroacetic acid afforded the best results in terms of yield, but with poor enantioselectivity (18 and 30% ee, respectively) with both acids (Scheme 3). However, moderate yields and high enantioselectivities, 83% and 97% ee, were obtained in the case of β-keto sulfone **2j** when trifluoroacetic acid and trifluoromethanesulfonic acid, respectively, were employed (Scheme 3). Other attempts to obtain enantioenriched alkylation products using these benzylic alcohols and activated methylene compounds by changing temperature, catalyst loading, or other reaction parameters were ineffective.

Finally, allylic alcohols, which also would produce a rather stable carbocationic intermediates after dehydration,[11] were also examined, since their use as alkylating agents would be very attractive because it would represent a metal-free asymmetric Tsuji–Trost-type reaction.[12] Thus, activated methylene compounds **2a**,**b**,**f**,**g**,**i**,**j**, which afforded the best results in terms of enantioselection in their reaction with benzylic alcohols, were subjected to the optimized reaction conditions using allylic alcohols **4a** and




**Scheme 2** Asymmetric alkylation of activated methylene compounds with **1a**




**Scheme 3** Asymmetric alkylation of activated methylene compounds with 9*H*-thioxanthen-9-ol

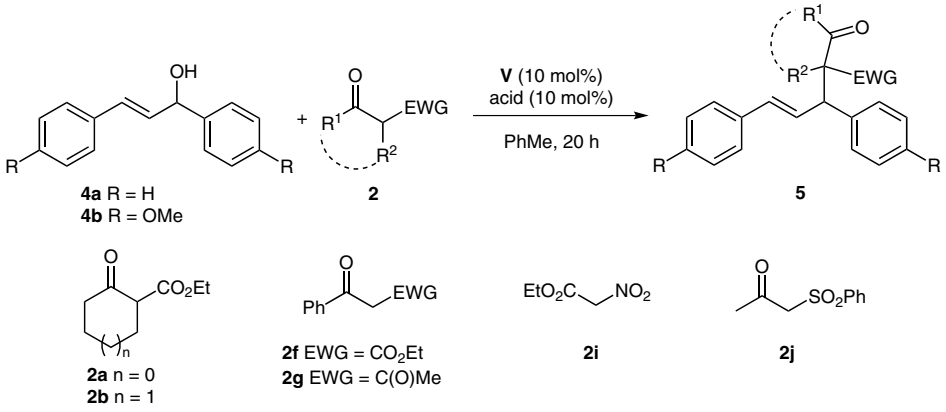
**4b** as electrophiles (Scheme 4). With alcohol **4a**, which forms highly reactive carbocationic intermediate ($E$ = 2.70),[9] excellent yields, although with almost no enantioselection (<10% ee), were observed in most cases despite the use of different temperatures and catalyst loading. Slightly better results, which could be ascribed to the formation of a more stable allylic carbocation after dehydration ($E$ = –1.45)[9] were observed with (*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-ol (**4b**), although from all the methylene compounds **2a**,**b**,**f**,**g**,**i**,**j** examined, cyclic β-keto esters were the only substrates that yielded the corresponding enantioenriched allylation products (Scheme 4 and Table 3). Thus, the reaction between **4b** and keto ester **2a** gave **5ba** in good yields and modest diastereo- and enantioselectivity employing either acid when the reaction was carried out at –50 °C (Table 3, entries 1 and 2). It is remarkable that depending on the acid employed the opposite diastereomeric ratio was observed for product **5ba**. After several attempts we were able to slightly increase the enantioselectivity of one of the diastereomers in the case of using trifluoroacetic acid (up to 50% ee) by lowering the temperature (–78 °C) and increasing the amount of catalyst to 20 mol% (entry 3). Unfortunately, under these new conditions, trifluoromethanesulfonic acid produced inferior results (entry 4). Next, β-keto ester **2b** was also tested and under the optimal reaction conditions and it gave the corresponding product **5bb** in modest yield and low diastereo- and enantioselectivity in its best result with either acid (entries 5 and 6). Further changes in the reaction conditions in order to improve these results were unsuccessful. In addition, as already mentioned, the reaction between **4b** and **2f**,**g**,**i** produced the desired products in high yields, but as racemic mixtures; the reaction with **2j** failed.

**Table 3** Asymmetric Alkylation of **4b** with Active Methylene Compounds[a]

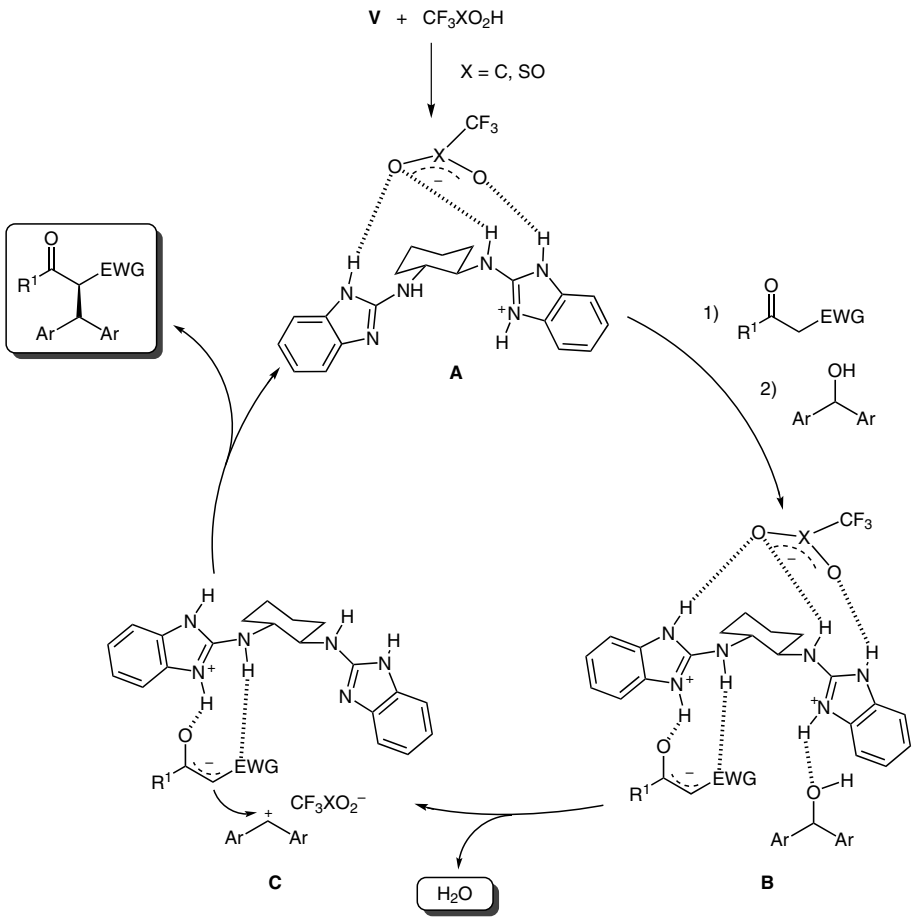
| Entry | Acid | Temp (°C) | Product | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | TFA | –50 | **5ba** | 64 | 70:30 | 26:24 |
| 2 | TfOH | –50 | **5ba** | 72 | 25:75 | 40:30 |
| 3 | TFA[e] | –78 | **5ba** | 72 | 73:27 | 48:12 |
| 4 | TfOH[e] | –78 | **5ba** | 30 | 55:45 | 30:28 |
| 5 | TFA | –20 | **5bb** | 67 | 63:37 | 5:10 |
| 6 | TfOH | –20 | **5bb** | 55 | 52:48 | 5:25 |

[a] Reaction conditions: **4b** (0.15 mmol), **2** (0.23 mmol, 1.5 equiv), catalyst **V** (10 mol%), acid (10 mol%) toluene (1.0 mL), unless otherwise stated.
[b] Isolated yield after preparative TLC.
[c] Determined by $^1$H NMR analysis of crude product.
[d] Determined by HPLC using chiral columns (see Supporting Information for details).
[e] 20 mol% of catalyst **V** and acid were employed.

Concerning the reaction mechanism for benzylic alcohols, an $S_N1$-type mechanism was immediately assumed from the fact that as soon as alcohol **1a** was added to the solution containing the catalyst and the acid, it turned deep blue, indicating the formation of the corresponding cationic specie (Michler's hydrol blue),[9] remaining this color until the reaction went to completion. In addition, the




**Scheme 4** Asymmetric allylation of activated methylene compounds with allylic alcohols **1d** and **1e**




**Scheme 5** Proposed reaction mechanism for benzylic alcohols

comparison of HPLC chart of compound **3af** with our previous copper-catalyzed work (in which *R*-configuration was assumed)[6] points towards the *S*-configured product **3af** when (*R*,*R*)-**V** was used. These facts, along with previous experimental and computational studies carried out in our group on the use of organocatalyst catalyst **V** in the presence of an acid for the Michael addition of 1,3-dicarbonyl compounds to maleimides,[8e,f] led us to propose a catalytic cycle as shown in Scheme 5. Thus, after mixing pre-catalyst **V** and equimolecular amounts of the corresponding acid, the bifunctional catalytic species **A** is formed through protonation of the most basic iminic nitrogen. Subsequent addition of activated methylene compound and benzylic alcohol would give rise to the formation of intermediate **B**, through dual hydrogen bond activation. After dehydration, presumably an ionic pair is formed which would react in an enantioselective fashion with the methylene compound (intermediate **C**), releasing the product and recovering the catalytic species **A**.

According to the above-proposed reaction mechanism, after the reaction takes place, the catalyst **V** remains protonated. Therefore, taking advantage on this purported fact, we studied the possible recovery and reutilization of the (*R*,*R*)-bis(2-aminobenzoimidazole) catalyst **V**. Thus, we performed a 1-mmol scale model reaction (Scheme 1) and after the work-up, the aqueous phase was treated with saturated aqueous sodium hydrogen carbonate until basic pH, recovering the organocatalyst **V** in 62% yield after extraction in dichloromethane. The catalyst was again reused without further purification in the same reaction, and no apparent loss of catalytic activity was observed.

In summary, the first metal-free asymmetric alkylation of activated methylene compounds with benzylic alcohols can be performed using $C_2$ symmetric bis(2-aminobenzoimidazole) **V** as a bifunctional organocatalyst. The corresponding alkylated products were obtained generally in good yields and with moderate to high enantioselectivities. Despite the fact that the reaction seems to be almost exclusively limited to highly activated alcohols, the methodology presented here can be considered as complementary to the metal-catalyzed processes which was only useful with xanthenols. According to our observations, apparently the reaction proceeds through a dual hydrogen-bond activation, in an $S_N1$-type mechanism, in which the activated methylene compound reacts in an enantioselective manner with the in situ formed benzylic carbocation. In addition, we have demonstrated that the organocatalyst **V** can be recovered and reused without any loss of activity. Finally, the basis for an asymmetric organocatalyzed



Tsuji–Trost-type reaction with allylic alcohols is established.

All reagents were purchased from commercial sources and used without further purification. Substrates which were not commercially available were synthesized according to known literature procedures.[13] Catalysts **II**–**VI** were synthesized as described in the literature and the spectroscopic data fully agreed with the reported values.[8b,e] Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. IR spectra were recorded on a Jasco FT-IR 4100 LE (Pike Miracle ATR) and only the structurally most relevant peaks are listed. NMR spectroscopy was performed on a Bruker AC-300 or a Bruker Avance-400 using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. LR-MS (EI) were obtained at 70 eV on an Agilent GC/MS-5973N instrument equipped with a HP-5MS column (Agilent Technologies, 30 m × 0.25 mm) and HRMS (ESI) were obtained on a Waters LCT Premier XE instrument equipped with a time-of-flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model Waters Acquity H Class. Optical rotations were measured on a Jasco P-1030 polarimeter with a 5-cm cell (*c* given in g/100 mL). Enantioselectivities were determined by HPLC analysis (Agilent 1100 Series HPLC) equipped with a G1315B diode array detector and a Quat Pump G1311A equipped with the corresponding Daicel chiral column. Analytical TLC was performed on Merck silica gel plates and the spots were visualized with UV light at 254 nm. Silica gel 60 $F_{254}$ containing gypsum was employed for preparative layer chromatography.

**Asymmetric Alkylation of Activated Methylene Compounds with Alcohols; General Procedure**

In an open-air flask the corresponding acid co-catalyst TFA or TfOH (0.015 mmol, 10 mol%) was added to a solution of bis(2-aminobenzoimidazole) **V** (0.015 mmol, 10 mol%) in technical grade toluene (0.5 mL). After 5 min the turbid solution became transparent. Next, the flask was placed in a cooling bath at the corresponding temperature, and then the activated methylene compound (0.23 mmol, 1.5 equiv) was added and after an additional 5 min, a solution of the corresponding alcohol (0.15 mmol) in toluene (0.5 mL) was finally added by syringe. The mixture was stirred for 20 h. After this time, $H_2O$ (5 mL) and EtOAc (5 mL) were added at r.t. The aqueous layer was re-extracted (2 × 5 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Finally, the reaction crude was purified by preparative TLC (hexanes–EtOAc).

For the recovery of the organocatalyst **V**, after the reaction work-up, the aqueous phase was treated with sat. aq $NaHCO_3$ until basic pH. The aqueous phase was then extracted with $CH_2Cl_2$ (3 × 5 mL), dried ($MgSO_4$) and evaporated to afford **V** in 62% yield.

**Ethyl 1-{Bis[4-(dimethylamino)phenyl]methyl}-2-oxocyclopentanecarboxylate (3aa)**

Yellow solid; yield: 55 mg (90%); 82% ee (after recrystallization); mp 207–210 °C (hexanes); $R_f$ = 0.25 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–EtOH, 92:8, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 24.5 (minor), 31.1 min (major).

$[\alpha]_D^{20}$ +129.6 (*c* 0.95, $CHCl_3$).

IR (KBr): 1100, 1134, 1222, 1348, 1444, 1519, 1644, 2088, 3442 $cm^{-1}$.

$^1H$ NMR (300 MHz): δ = 0.91 (t, *J* = 7.1 Hz, 3 H), 1.55–1.59 (m, 2 H), 1.67–1.78 (m, 2 H), 2.22–2.27 (m, 2 H), 2.87 (s, 6 H), 2.89 (s, 6 H), 3.86–4.02 (m, 2 H), 5.07 (s, 1 H), 6.56 (d, *J* = 8.7 Hz, 2 H), 6.63 (d, *J* = 8.7 Hz, 2 H), 6.95 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H).

$^{13}C$ NMR (75 MHz): δ = 13.7, 19.8, 29.2, 38.8, 40.5, 40.7, 53.5, 61.5, 79.8, 112.2, 112.5, 129.0, 129.5, 130.7, 148.9, 168.0, 214.3.

MS (IE): *m*/*z* (%) = 408 [$M^+$, 3], 254 (100), 237 (14), 210 (25), 134 (15), 126 (12).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + H] calcd for $C_{25}H_{33}N_2O_3$: 409.2491; found: 409.2491.

**Ethyl 1-{Bis[4-(dimethylamino)phenyl]methyl}-2-oxocyclohexanecarboxylate (3ab)**

Colorless oil; yield: 44 mg (70%); 90% ee; $R_f$ = 0.27 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–*i*-PrOH, 97:3, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 14.7 (major), 17.0 min (minor).

$[\alpha]_D^{20}$ +292.4 (*c* 1.4, $CHCl_3$).

IR (ATR): 1127, 1163, 1199, 1229, 1346, 1444, 1478, 1518, 1561, 1611, 1710, 2340, 2358, 2798.2, 2863, 2935 $cm^{-1}$.

$^1H$ NMR (300 MHz): δ = 0.96 (t, *J* = 7.1 Hz, 3 H), 1.20–1.30 (m, 2 H), 1.60–1.78 (m, 3 H), 2.37–2.44 (m, 2 H), 2.62–2.67 (m, 1 H), 2.87 (s, 12 H), 3.77–3.83 (m, 1 H), 3.89–3.95 (m, 1 H), 4.89 (s, 1 H), 6.60 (d, *J* = 8.8 Hz, 4 H), 7.22–7.27 (m, 4 H).

$^{13}C$ NMR (75 MHz): δ = 13.6, 22.7, 26.7, 34.4, 40.6, 40.7, 41.9, 61.1, 66.4, 77.2, 112.1, 112.2, 127.5, 129.3, 129.5, 130.8, 131.2, 147.9, 148.8, 149.1, 170.9, 206.9.

MS (EI): *m*/*z* (%) = 422 [$M^+$, 4], 254 (100), 253 (79), 237 (14), 210 (25), 126 (13), 118 (11).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + H] calcd for $C_{26}H_{35}N_2O_3$: 423.2648; found: 423.2648.

**3-Acetyl-3-{bis[4-(dimethylamino)phenyl]methyl}tetrahydrofuran-2-one (3ae)**

Yellow oil; yield: 46 mg (81%); 26% ee; $R_f$ = 0.25 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–EtOH, 96:4, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 22.0 (major), 56.6 min (minor).

$^1H$ NMR (300 MHz): δ = 1.98–2.42 (m, 1 H), 2.45(s, 3 H), 2.73–2.84 (m, 1 H), 2.89 (s, 6 H), 2.92 (s, 6 H), 3.57–3.62 (m, 1 H), 4.02–4.08 (m, 1 H), 5.18 (s, 1 H), 6.58–6.64 (m, 4 H), 6.97–7.00 (m, 4 H).

$^{13}C$ NMR (75 MHz): δ = 23.6, 25.3, 40.4, 52.7, 66.5, 67.3, 112.3, 112.6, 127.1, 127.8, 129.4, 130.1, 149.2, 149.4, 175.5, 199.9, 201.9.

MS (EI): *m*/*z* (%) = 380 [$M^+$, 6], 255 (17), 254 (100), 253 (78), 237 (14), 210 (26), 134 (15), 126 (10).

**Ethyl 2-Benzoyl-3,3-bis[4-(dimethylamino)phenyl]propanoate (3af)[6]**

Brown solid; yield: 44.7 mg (70%); 38% ee; mp 179–180 °C. Chiral HPLC analysis (Chiralcel ODH column, hexane–*i*-PrOH, 96:4, flow rate = 0.8 mL/min, λ = 254 nm): $t_R$ = 17.70 (major), 20.75 min (minor).

$[\alpha]_D^{20}$ –11.78 (*c* 1, $CHCl_3$).

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.1 Hz, 3 H), 2.79 (s, 6 H), 2.88 (s, 6 H), 3.89–3.94 (m, 2 H), 4.91 (d, *J* = 11.7 Hz, 1 H), 5.31 (d, *J* = 11.7 Hz, 1 H), 6.57 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 7.08 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 7.42–7.45 (m, 3 H), 8.00–8.04 (m, 2 H).

$^{13}C$ NMR (75 MHz): δ = 13.8, 40.6, 49.2, 60.1, 61.3, 112.8, 112.9, 128.1, 128.5, 128.7, 130.6, 133.2, 136.9, 149.0, 149.3, 168.1, 193.3.

MS (EI): *m*/*z* (%) = 444 [$M^+$, 1], 255 (18), 254 (100), 253 (79), 237 (15), 210 (25), 134 (15).

**2-{Bis[4-(dimethylamino)phenyl]methyl}-1-phenylbutane-1,3-dione (3ag)**

Yellow oil; yield: 59 mg (95%); 87% ee; $R_f$ = 0.56 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–EtOH, 92:8, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 32.71 (minor), 35.92 min (major).

$[\alpha]_D^{20}$ –10.7 (*c* 1.1, $CHCl_3$).

IR (ATR): 1062, 1166, 1261, 1276, 1446, 1480, 1519, 1612, 1674, 1720, 2361, 2801, 2852, 2923, 2987, 3005 $cm^{-1}$.

$^1H$ NMR (300 MHz): δ = 2.04 (s, 3 H), 2.79 (s, 6 H), 2.89 (s, 6 H), 4.93 (d, *J* = 12.0 Hz, 1 H), 5.51 (d, *J* = 12.0 Hz, 1 H), 6.50 (d, *J* = 8.7 Hz, 2 H), 6.65 (d, *J* = 8.7 Hz, 2 H), 7.06 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.41 (m, 2 H), 7.50–7.55 (m, 1 H), 7.91–8.00 (m, 2 H).

$^{13}C$ NMR (75 MHz): δ = 27.5, 40.6, 49.8, 69.7, 112.8, 112.9, 127.8, 128.1, 128.2, 128.6, 128.6, 128.8, 133.3, 195.3, 201.0.

MS (EI): *m*/*z* (%) = 414 [$M^+$, 1], 255 (18), 254 (100), 253 (78), 237 (15), 210 (28), 134 (17), 126 (13), 118 (11).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + H] calcd for $C_{27}H_{31}N_2O_2$: 415.2386; found: 415.2386.

**2-Acetyl-2-{bis[4-(dimethylamino)phenyl]methyl}cyclopentanone (3ah)**

Colorless oil; yield: 34 mg (60%); 18% ee; $R_f$ = 0.55 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel ASH column, hexane–*i*-PrOH, 97/3, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 6.78 (minor), 7.81 min (major).

$^1H$ NMR (300 MHz): δ = 1.63–1.75 (m, 2 H), 2.00–2.17 (m, 2 H), 2.10 (s, 3 H), 2.33–2.42 (m, 2 H), 2.86 (s, 6 H), 2.88 (s, 6 H), 5.17 (s, 1 H), 6.55–7.04 (m, 6 H), 7.73–7.78 (m, 2 H).

$^{13}C$ NMR (75 MHz): δ = 20.2, 25.8, 26.1, 27.3, 40.5, 53.8, 62.7, 128.2, 128.5, 128.7, 129.3, 129.4, 129.5, 130.4, 149.0, 190.5, 203.4.

MS (EI): *m*/*z* (%) = 378 [$M^+$, 0.5], 281 (35), 254 (64), 253 (69), 237 (13), 208 (21), 207 (100), 191 (15), 134 (12).

**Ethyl 3,3-Bis[4-(dimethylamino)phenyl]-2-nitropropanoate (3ai)**

Yellow oil; yield: 41 mg (71%); 26% ee; $R_f$ = 0.32 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel ADH column, hexane–*i*-PrOH, 96:4, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 30.89 (minor), 41.31 min (major).

IR (ATR): 1061, 1096, 1130, 1162, 1311, 1351, 1444, 1518, 1559, 1611, 1746, 2341, 2360, 2802, 2851, 2921, 2975 $cm^{-1}$.

$^1H$ NMR (300 MHz): δ = 1.05 (t, *J* = 7.1 Hz, 3 H), 2.88 (s, 12 H), 4.05 (qd, *J* = 7.1, 2.7 Hz, 2 H), 4.83 (d, *J* = 12 Hz, 1 H), 5.82 (d, *J* = 12 Hz, 1 H), 6.63 (dd, *J* = 8.8, 4.2 Hz, 4 H), 7.13 (m, 4 H).

$^{13}C$ NMR (75 MHz): δ = 13.6, 40.4, 40.5, 62.7, 77.2, 91.8, 112.7, 112.8, 125.8, 126.6, 127.9, 128.7, 149.7, 149.8, 163.5.

MS (EI): *m*/*z* (%) = 385 [$M^+$, 4], 255 (17), 254 (100), 253 (81), 237 (12), 210 (25), 207 (14), 134 (17), 126 (13).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + H] calcd for $C_{21}H_{28}N3O_4$: 386.2080; found: 386.2080.

**4,4-Bis[4-(dimethylamino)phenyl]-3-(phenylsulfonyl)butan-2-one (3aj)**

Brown solid; yield: 37 mg (51%); 48% ee; mp 202–204 °C; $R_f$ = 0.57 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–EtOH, 70:30, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 19.32 (major), 81.42 min (minor).

$[\alpha]_D^{20}$ +7.3 (*c* 0.6, $CHCl_3$).

IR (ATR): 1135, 1245, 1294, 1348, 1447, 1516, 1608, 1720, 2339, 2355, 2796, 2852, 2922, 2948 $cm^{-1}$.

$^1H$ NMR (300 MHz): δ = 2.23 (s, 3 H), 2.84 (s, 12 H), 4.53 (d, *J* = 12.2 Hz, 1 H), 5.04 (d, *J* = 12.2 Hz, 1 H), 6.38 (d, *J* = 8.8 Hz, 2 H), 6.54 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 7.26–7.46 (m, 5 H).

$^{13}C$ NMR (75 MHz): δ = 29.7, 40.4, 40.6, 49.5, 80.5, 112.7, 112.8, 127.3, 128.2, 128.4, 128.5, 128.6, 133.0, 139.6, 149.4, 149.5, 199.6.

MS (EI): *m*/*z* (%) = 450 [$M^+$, 2], 255 (18), 254 (100), 253 (80), 237 (15), 210 (24), 134 (16), 126 (15), 118 (11).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + H] calcd for $C_{26}H_{31}N_2O_3S$: 451.2055; found: 451.2043.

**Ethyl 2-Oxo-1-(9*H*-thioxanthen-9-yl)cyclopentanecarboxylate (3ca)**[6]

Yellow solid; yield: 37 mg (70%); 18% ee; mp 73–74 °C; $R_f$ = 0.37 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–EtOH, 99.5:0.5, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 17.03 (minor), 18.10 min (major).

$^1H$ NMR (300 MHz): δ = 1.15 (t, *J* = 7.2 Hz, 3 H), 1.26–1.29 (m, 1 H), 1.62–1.78 (m, 3 H), 2.18–2.38 (m, 1 H), 2.57–2.83 (m, 1 H), 3.93–4.01 (m, 2 H), 5.23 (s, 1 H), 7.02–7.63 (m, 8 H).

$^{13}C$ NMR (75 MHz): δ = 13.9, 19.7, 28.7, 37.5, 50.2, 61.8, 69.6, 126.2, 126.6, 126.8, 127.2, 130.2, 131.3, 132.6.

MS (EI): *m*/*z* (%) = 352 [$M^+$, 2], 198 (16), 197 (100), 165 (8).

**1-(Phenylsulfonyl)-1-(9*H*-thioxanthen-9-yl)propan-2-one (3cj)**

White solid; yield: 41 mg (69%); 97% ee; mp 153–154 °C; $R_f$ = 0.58 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel ODH column, hexane–*i*-PrOH, 92:8, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 13.98 (minor), 26.47 min (major).

$[\alpha]_D^{20}$ +6.96 (*c* 1, $CHCl_3$).

IR (ATR): 1073, 1083, 1146, 1272, 1307, 1325, 1358, 1443, 1464, 1584, 1721, 2162, 2192, 2341, 2336, 2931, 2970, 3011, 3063 $cm^{-1}$.

$^1H$ NMR (300 MHz): δ = 1.79 (s, 3 H), 5.13 (d, *J* = 11.0 Hz, 1 H), 5.31 (d, *J* = 11.0 Hz, 1 H), 7.06–7.30 (m, 7 H), 7.32–7.46 (m, 4 H), 7.63–7.66 (m, 2 H).

$^{13}C$ NMR (75 MHz): δ = 33.1, 48.3, 69.0, 126.9, 127.2, 127.3, 127.5, 127.6, 127.7, 128.7, 130.1, 131.6, 133.1, 133.8.

MS (EI): *m*/*z* (%) = 394 [$M^+$, 2], 198 (15), 197 (100), 165 (10).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + Na] calcd for $C_{22}H_{18}O_3S_2Na$: 417.0595; found: 417.0596.

**Ethyl (*E*)-1-[1,3-Bis(4-methoxyphenyl)allyl]-2-oxocyclopentanecarboxylate (5ba)**

Colorless oil; yield: 44 mg (72%); 48% and 12% ee obtained as diastereomeric mixture 73:27 dr; $R_f$ = 0.38 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–EtOH, 96:4, flow rate = 1 mL/min, λ = 230 nm): $t_R$ = 13.97 (minor), 16.88 (major), 15.17 (major), 18.72 min (minor).

IR (ATR): 1103, 1137, 1265, 1402, 1420, 1462, 1607, 1718, 1748, 2835, 2932, 2957 $cm^{-1}$.

$^1H$ NMR (400 MHz): δ = 1.10 (t, *J* = 7.1 Hz, 3 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 1.65–1.89 (m, 4 H), 2.05–2.25 (m, 4 H), 2.35–2.42 (m, 2 H), 2.68–2.73 (m, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.98–4.18 (m, 4 H), 4.35 (m, 1 H), 4.49 (m, 1 H), 6.22–6.28 (m, 3 H), 6.44 (d, *J* = 15.7 Hz, 1 H), 6.79–6.83 (m, 8 H), 7.19–7.27 (m, 8 H).

$^{13}C$ NMR (100 MHz): δ = 13.9, 14.2, 19.6, 19.8, 28.4, 29.9, 38.9, 39.0, 51.4, 52.1, 55.2, 55.3, 61.6, 61.8, 66.3, 66.6, 113.7, 113.8, 113.84, 113.9, 125.5, 126.3, 127.5, 127.51, 128.2, 128.3, 128.5, 128.6, 129.5, 129.7, 129.8, 129.9, 130.7, 131.7, 131.9, 132.0, 132.2, 158.5, 159.1, 169.2, 213.6, 213.7.

MS (EI): *m*/*z* (%) = 408 [$M^+$, 1], 355 (17), 354 (100), 339 (13), 308 (12), 281 (14), 207 (10), 177 (20).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + Na] calcd for $C_{25}H_{28}O_5Na$: 431.1834; found: 431.1843.

**Ethyl (*E*)-1-[1,3-Bis(4-methoxyphenyl)allyl]-2-oxocyclohexanecarboxylate (5bb)**

Yellow oil; yield: 42 mg (67%); 5% and 10% ee obtained as diastereomeric mixture 63:37 dr; $R_f$ = 0.40 (hexane–EtOAc, 4:1). Chiral HPLC analysis (Chiralcel IA column, hexane–EtOH, 98:2, flow rate = 1 mL/min, λ = 254 nm): $t_R$ = 12.78 (major), 15.51 (minor), 14.24 (minor), 18.18 min (major).

IR (ATR): 1092, 1131, 1176, 1202, 1248, 1299, 1365, 1441, 1463, 1509, 1578, 1607, 1710, 2835, 2863, 2935, 3030 $cm^{-1}$.

$^1H$ NMR (300 MHz): δ = 1.06–1.112 (m, 6 H), 1.54–1.77 (m, 8 H), 1.93–1.95 (m, 2 H), 2.42–2.46 (m, 4 H), 2.56–2.59 (m, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.90–4.15 (m, 6 H), 6.28–6.34 (m, 2 H), 6.48–6.57 (m, 2 H), 6.78–6.82 (m, 8 H), 7.24–7.33 (m, 8 H).

$^{13}C$ NMR (75 MHz): δ = 13.9, 13.97, 22.7, 26.7, 27.0, 33.7, 34.9, 42.0, 52.4, 52.9, 55.1, 55.2, 55.3, 58.6, 60.4, 61.3, 65.9, 65.97, 66.1, 113.3, 113.4, 113.8, 114.8, 116.0, 126.9, 127.4, 127.5, 130.1, 130.2, 130.9, 131.1, 131.4, 131.5, 131.9, 132.3, 158.3, 158.4, 158.9, 159.0, 170.9, 191.6, 206.7, 206.9, 206.93.

MS (EI): *m*/*z* (%) = 422 [$M^+$, 0.3], 404 (18), 254 (22), 253 (100), 145 (23), 121 (12).

HRMS ($ESI^+$): *m*/*z* [$M^+$ + H] calcd for $C_{26}H_{30}O_5$: 423.2171; found: 423.2171.

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