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A Straightforward Organocatalytic Alkylation of 2-Arylacetaldehydes: An Approach towards Bisabolanes

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Abstract: A highly stereoselective organocatalytic α-alkylation of 2-arylacetaldehydes with a commercially available carbenium tetrafluoroborate is described. The stereoselective alkylation was carried out in acetonitrile/water, under air in the presence of a commercially available imidazolidinone (MacMillan's catalyst). Key intermediates for the synthesis of bisabolanes were obtained through a simple chemistry. In particular a direct, enantioselective and facile synthesis of (*R*)-(−)-curcumene is described.

Keywords: α-alkylation; bisabolanes; curcumene; enamines; Macmillan's catalyst; organocatalysis

Introduction

Several important classes of natural products, including bisabolanes, heliannanes, serrulatanes, and pseudopterosins, have a characteristic benzylic stereocenter carrying a methyl group (Figure 1).[1]

These compounds exhibit interesting and diverse biological activities, such as anti-inflammatory, antiviral, and anti-mycobacterial properties.[2] In addition, the natural products belonging to this class of bisabolane sesquiterpenes [e.g., (*R*)-(−)-curcumene (**I**), (*S*)-(+)-*ar*-turmerone (**II**) and bisacumol (**III**)] are key components of a large number of essential oils and they are also used as additives in perfumes and cosmetics.[3] For these reasons, these natural products have attracted considerable interest and several syntheses of the enantioenriched (*R*)-(−)-curcumene have been reported.[4] (*R*)-(−)-Curcumene has also been used as a starting material for the preparation of other bisabolanes and related terpenes.[5] In the past, the synthesis of the simple structure of bisabolanes involved considerable synthetic effort as it requires the configurational control at the benzylic stereogenic centre.

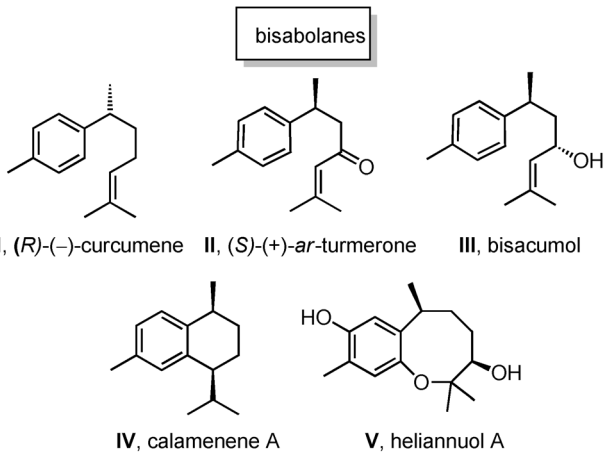
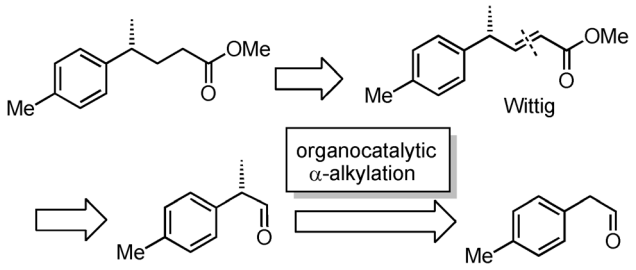


Figure 1. Different structures of bisabolanes.

Recently, organocatalysis[6] has reached a level of maturity at which it can be employed for the concise and selective total synthesis of natural products.[7] Organocatalysis has also been merged with organometallic methodologies by selection of compatible transition metal catalysts for use in combination with amino catalysis.[8]

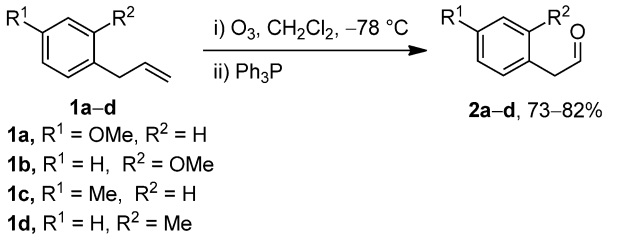
Following on from this concept, Córdova has described a concise and selective approach to bisabolanes based on the enantioselective β-alkylation of α,β-unsaturated aldehydes by a combination of amino catalysis and transition metal catalysis. This copper salt-catalysed asymmetric addition of dialkylzinc reagents to enals promoted by an organocatalyst gave up to 98:2 *er* and it was used as the key step for the efficient total synthesis of bisabolane sesquiterpenes.[9a] Another organocatalytic approach for the synthesis of benzylic stereogenic centeres uses iminium activation to enable stereoselective reduction of β-substituted α,β-enals.[9b,c]



Scheme 1. An organocatalytic approach to bisabolanes.

We have approached the organocatalytic installation of the benzylic stereogenic centre by considering an α-alkylation of aldehydes by a masked methyl group as proposed in Scheme 1. The analysis shows that the alkylated product can be transformed into the required intermediate by a simple chemistry.

Recently, our group[10] and other groups[11] have described organocatalytic S_N1-type reactions in which the challenging α-alkylation of aldehydes is made possible by the formation of stabilised carbenium ions and promoted by organocatalysis.[12] We have expanded the scope of the chemistry by using the commercially available 1,3-benzodithiolylium tetrafluoroborate.[13] The products obtained contain the benzodithiol group as a versatile building block[14] that can be easily transformed into the corresponding methyl group by treatment with Raney Ni or metallated by *n*-BuLi.[15] Herein, we report that stereoselective α-alkylation of benzylic aldehydes with benzodithiolylium tetrafluoroborate can be used to install the benzylic stereocentre in the synthesis of bisabolanes.



1a–d

1a, R^1 = OMe, R^2 = H
1b, R^1 = H, R^2 = OMe
1c, R^1 = Me, R^2 = H
1d, R^1 = H, R^2 = Me

2a–d, 73–82%

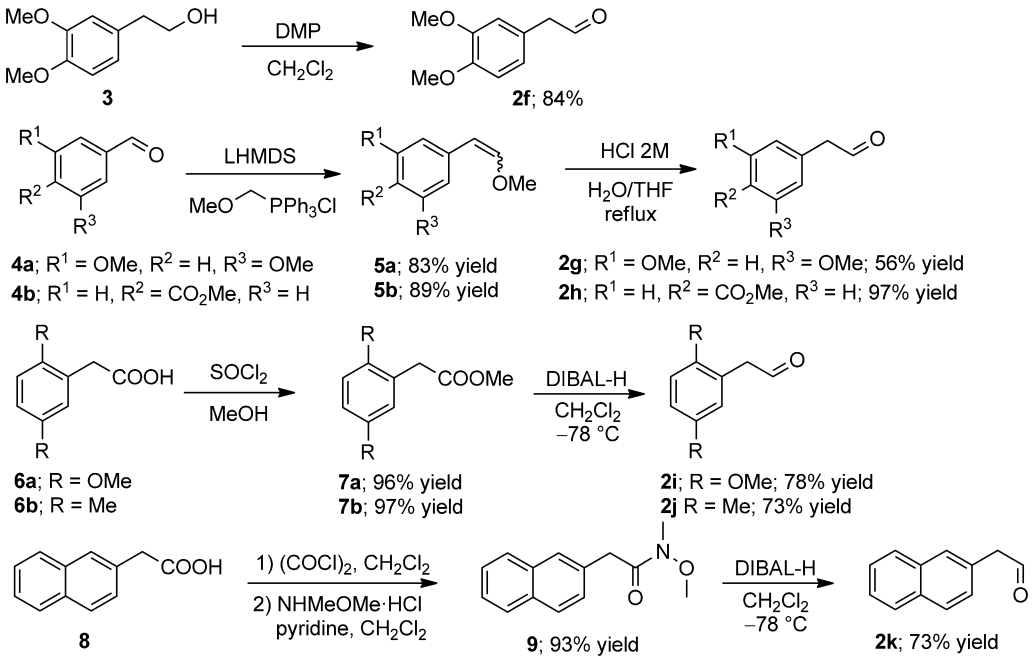
Scheme 2. Preparation of the arylacetaldehydes by ozonolysis.

Results and Discussion

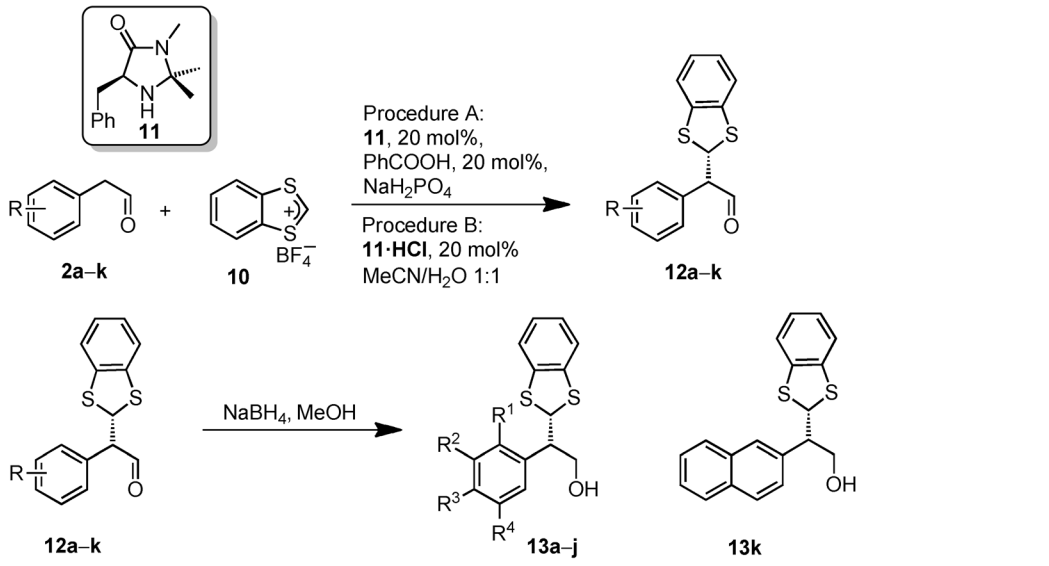
A variety of substituted 2-arylacetaldehydes, precursor of natural products[16] can be easily prepared by ozonolysis of the corresponding allyl derivatives. The commercially available allylic compounds **1a–d** (Scheme 2) were subjected to ozonolysis in the standard reaction conditions and the corresponding aldehydes **2a–d** were isolated in high yields after purification.

Phenylacetaldehyde **2e** was commercially available and it was used without any purification.

Different aryl-substituted substrates were also obtained through other simple methods (Scheme 3). The oxidation with Dess–Martin periodinane of the commercially available alcohol **3** gave the compound **2f** in good yield. The aldehydes **2g** and **2h** were obtained by a reaction of the phosphorus reagent with commercially available aldehydes **4a** and **4b**. The substituted



Scheme 3. Preparation of the aldehydes **2f–k**.



13a; R^1 = H, R^2 = H, R^3 = OMe, R^4 = H; 98% yield, 92% *ee* (Procedure A)
13b; R^1 = OMe, R^2 = H, R^3 = H, R^4 = H; 95% yield, 93% *ee* (Procedure A)
13c; R^1 = H, R^2 = H, R^3 = Me, R^4 = H; 95% yield, 94% *ee* (Procedure A)
13d; R^1 = Me, R^2 = H, R^3 = H, R^4 = H; 93% yield, 92% *ee* (Procedure A)
13e; R^1 = H, R^2 = H, R^3 = H, R^4 = H; 96% yield, 96% *ee* (Procedure A)
13f; R^1 = H, R^2 = OMe, R^3 = OMe, R^4 = H; 91% yield, 95% *ee* (Procedure B)
13g; R^1 = H, R^2 = OMe, R^3 = H, R^4 = OMe; 93% yield, 92% *ee* (Procedure B)
13h; R^1 = H, R^2 = H, R^3 = CO_2Me, R^4 = H; 96% yield, 82% *ee* (Procedure B)
13i; R^1 = OMe, R^2 = H, R^3 = H, R^4 = OMe; 93% yield, 96% *ee* (Procedure B)
13j; R^1 = Me, R^2 = H, R^3 = H, R^4 = Me; 94% yield, 97% *ee* (Procedure B)
13k; 94% yield, 94% *ee* (Procedure B)

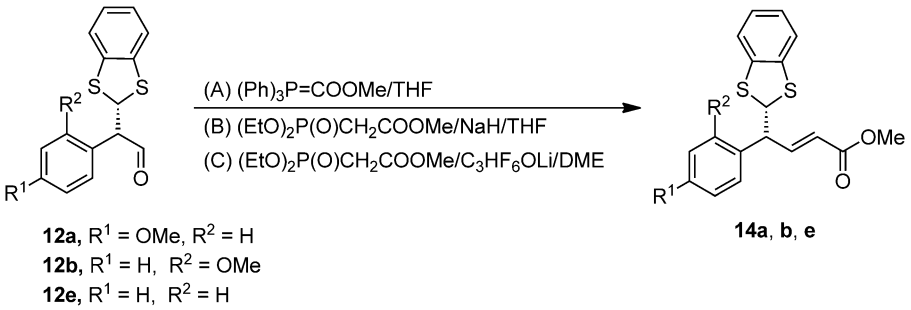
Scheme 4. Reaction sequence for the synthesis of the key intermediates **13a–k**.

acetaldehydes **2i–k** were obtained by transformation of the corresponding acids **6a**, **6b** and **8** into methyl esters **7a**, **7b** or the Weinreb amide **9**[17] followed by reduction with DIBAL-H.

After purification by distillation or chromatography, these 2-arylacetaldehydes **2a–k** were reacted with the commercially available 1,3-benzodithiolylium tetrafluoroborate **10** in CH_3CN/H_2O, employing the MacMillan imidazolidinone **11** as a catalyst (20 mol%) in the presence or in the absence of inorganic bases. This convenient procedure (procedure B), that use the commercially available MacMillan catalyst **11** as hydrochloride salt, can give high yields and high reproducibility in the alkylation of aldehydes, if the organic solvent is evaporated under reduced pressure at room temperature before adding MeOH for the reduction with $NaBH_4$. Using both the procedures excellent yields and high stereocontrol were observed in all cases tested. The enantiomeric excesses of the alkylated products (Scheme 4) were determined after reduction of the crude product with $NaBH_4$ (see the Supporting Information for traces of HPLC analysis). The desired products **13a–k** were obtained in high yields and stereoselectivities by using a slight excess of aldehyde (1 equiv.) with respect to the benzodithiolylium **10**. The substitution pattern of the aldehydes does not influence the stereochemical outcome of the reaction, and only in the case of the aryl acetaldehyde bearing an electron-withdrawing group (COOMe, **2h**) was the corresponding adduct **13h** isolated with an inferior enantiomeric excess. Especially noteworthy, the presence of an electron-donating MeO group in different positions is compatible with this alkylation and allows the preparation of useful intermediates for synthesis of bisabolanes.[18] In addition, the absence of electronic effects due to aromatic electron-rich aldehydes was also observed. The enantiomeric excesses of the isolated products were all above the 92% except with the aldehyde **12h**. Considering the mild reaction conditions and the effectiveness, this method is overpassing the stereoselective alkylations employing Evans' auxiliary.[19]

In order to prepare the bisabolane skeleton, crude products **12a**, **b**, **e** were reacted with Witting and Horner–Wadsworth–Emmons reagents (Scheme 5), by using different reaction conditions.

Unfortunately, in all cases a severe decrease in the enantiomeric excess of the isolated final products was observed (Table 1), compare to the starting material (from 92–96% to 24–82% *ee*).



12a, R^1 = OMe, R^2 = H
12b, R^1 = H, R^2 = OMe
12e, R^1 = H, R^2 = H

14a, **b**, **e**

Scheme 5. Elongation of compounds **12a**, **b**, **e** by Wittig-type reactions.

Table 1. Reaction of **12a**, **b**, **e** with different Wittig reagents and conditions.

Entry	Conditions	Substrate	*ee* of **12**[a]	*ee* of **14**[a]
1	A	**12a**	92	80
2	A	**12b**	93	82
3	A	**12e**	96	76
4	B	**12a**	92	81
5	C	**12a**	92	24

[a] The *ee* values were determined by HPLC analysis. See the Supporting Information for details.

Several slightly different reaction conditions, by varying solvents and temperature were examined, but again, the decrease in enantiomeric excess was always recorded. This behaviour was probably due to the increased acidity of the α-substituted benzodithiol aldehydes.[20]

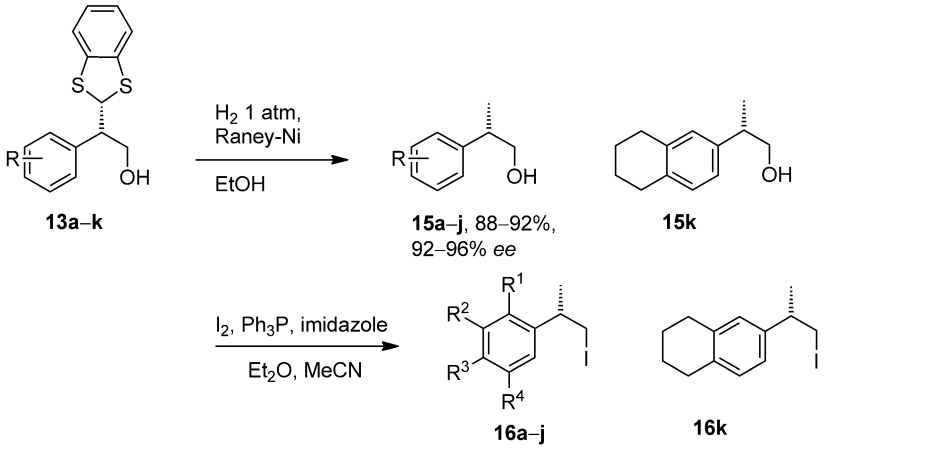
Therefore, we considered another synthetic approach to install the 2-carbon chain. It was found that, to avoid racemisation, it was necessary to transform the 1,3-benzodithiol group into a methyl group before performing the chain elongation. In order to reduce the amount of functional group manipulation and avoid numerous oxidation or reduction steps, we have replaced the HWE and Wittig reactions with a more efficient strategy, illustrated in Scheme 6 and Scheme 7.

This strategy considers the simple formation of iodo derivatives, and their successive reaction with nucleophiles. The alcohol derivatives **15a–k** were isolated and treated with Raney nickel to generate the corresponding methyl group. The reaction afforded good yields for all derivatives, with no racemisation. It is worth mentioning that the oxidation of the derivatives **15a–k** provides a straightforward access to the arylpropionic acids, which constitute an important class of anti-inflammatory drugs.[21] Recently, MacMillan published organocatalytic and organometallic approaches for the α-arylation of acidic derivatives.[22]

The α-methyl derivatives **15a–k** were converted into the corresponding iodides **16a–k** by a quite simple and known procedure.[23] However, the successive elongation of two carbon atoms, in order to obtain the key intermediates for bisabolanes synthesis was proven to be rather challenging. Indeed, the logical S_N2-type addition of the enolate derivatives failed. In particular, the addition of *tert*-butyl acetate enolates in the presence of DPMU or HMPA, under different conditions, temperature, or solvents, gave no traces of the desired product. Otherwise, in the examined reaction conditions we have principally isolated the eliminated product (β-methylstyrene), formed by elimination of HI from **16a–e**. We reasoned to use a more nucleophilic and less basic enolate such as a malonate. Following the straightforward methodology described recently by List,[24] we have obtained elongation by reacting the iodide derivatives with sodium malonate in DMF at room temperature (Scheme 7).

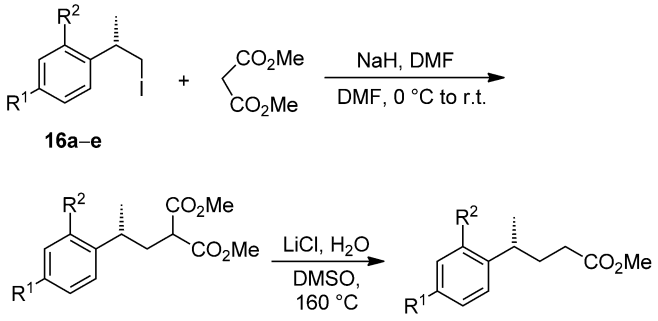
This strategy provides good reproducible yields in all the examined cases and it is also quite straightforward to perform it using inexpensive reagents. No additives, peculiar solvent mixtures or reduced temperatures are necessary to obtain the desired products. The malonate adducts **17a–e** were decarboxylated by the standard Krapcho procedure,[25] affording the products **18a–e** in high yields. With the final isolated products **18a–e** HPLC analysis proved that the entire reaction sequence was achieved without any racemisation. The methyl ester **18c** was previously used as a key intermediate in the synthesis of (*R*)-(−)-curcumene and (*R*)-(−)-erogorgiaene (Scheme 8).[26]

This synthesis was however, not straightforward and additional steps were required for the total synthesis of curcumene. In fact, the isolated **18c** needs to be transformed into the corresponding aldehyde through a reduction/oxidation sequence, and finally, after purification,[27] the intermediate aldehyde, is reacted with a Wittig reagent. We want to consider a more direct and simple approach towards curcumene, taking advantage of the availability and reactivity of the iodide **16c** and considerably shorten the total synthesis. By inspection of the curcumene molecule it is quite easy to design a retrosynthesis proposal



16a; R^1 = H, R^2 = H, R^3 = OMe, R^4 = H; 48% yield
16b; R^1 = OMe, R^2 = H, R^3 = H, R^4 = H; 50% yield
16c; R^1 = H, R^2 = H, R^3 = Me, R^4 = H; 50% yield
16d; R^1 = Me, R_2 = H, R^3 = H, R^4 = H; 50% yield
16e; R^1 = H, R^2 = H, R^3 = H, R^4 = H; 49% yield
16f; R^1 = H, R^2 = OMe, R^3 = OMe, R^4 = H; 86% yield
16g; R^1 = H, R^2 = OMe, R^3 = H, R^4 = OMe; 90% yield
16h; R^1 = H, R^2 = H, R^3 = CO_2Me, R^4 = H; 84% yield
16i; R^1 = OMe, R^2 = H, R^3 = H, R^4 = OMe; 85% yield
16j; R^1 = Me, R^2 = H, R^3 = H, R^4 = Me; 72% yield
16k; 72% yield

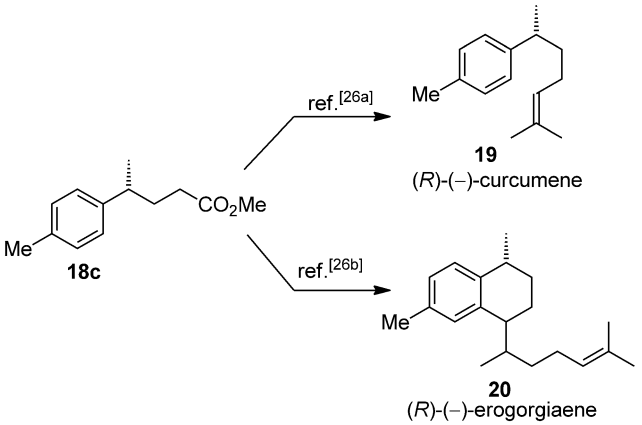
Scheme 6. Synthesis of the iodides **16a–k**.



17a; 85% yield
17b; 82% yield
17c; 84% yield
17d; 84% yield
17e; 83% yield

18a; R^1 = OMe, R^2 = H; 80% yield, 92% *ee*
18b; R^1 = H, R^2 = OMe; 81% yield, 91% *ee*
18c; R^1 = Me, R^2 = H; 80% yield, 89% *ee*
18d; R^1 = H, R^2 = Me; 82% yield, 94% *ee*
18e; R^1 = H, R^2 = H; 83% yield, 96% *ee*

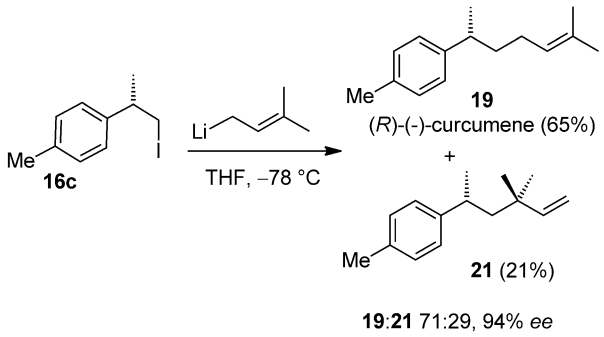
Scheme 7. Elongation by two carbons via reaction of iodides **16a–e** with malonate ion and successive decarboxylation.



Scheme 8. Published synthetic routes to bisabolanes starting from ester **18c**.

for the addition of prenylic nucleophilic reagents to the iodide **16c**.

Therefore, we have investigated the reaction of iodide derivatives **16c** and **16e** with different nucleophilic prenylic reagents (see the Supporting Information for details). We found that prenyl copper or high order allyl cyanocuprate[28] were giving low conversions and regioselectivity. By varying the reaction conditions, or performing the reaction at different temperatures, the desired adduct was always obtained in a low quantity. A moderate ratio (up to 1.5:1) in favour of the desired α-adduct **19** (Scheme 8) was afforded when prenyllithium, obtained by treatment of prenyl-tributylstannane with *n*-BuLi or MeLi, was reacted with racemic **16e**. When the same reaction was performed with **16c** (*ee* 95%), the desired adduct was obtained in quantitative yield as a 71:29 mixture of α and γ adducts.



Scheme 9. A direct and straightforward synthesis of (*R*)-(−)-curcumene.

The reaction of prenyllithium with **16c** gave a direct and rapid approach towards (*R*)-(−)-curcumene (Scheme 9). The mixture of α and γ adducts **21** and **19**, obtained in 86% yield, was easily separated by preparative TLC using hexane as eluent.

Conclusions

In conclusion, we have developed a robust approach towards the α-alkylation of 2-arylacetaldehydes variously substituted, using an organocatalytic procedure to prepare key chiral intermediates in the synthesis of bisabolanes. The advantages of this approach include the possibility to use the key intermediates **12a–k** formed for other transformations. The enantioenriched iodo derivative **16c**, obtained by a direct iodination of **15c**, was used for a short synthesis of (*R*)-(−)-curcumene (five total steps). Further studies are underway in our laboratory into the application of this methodology in the stereoselective total syntheses of various other natural products.

Experimental Section

General Methods

^{1}H NMR spectra were recorded on Varian Gemini 200 and Varian MR 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (*J* Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian MR 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ = 77.0 ppm). LC-electrospray ionisation mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240–400 mesh silica gel. Determinations of enantiomeric excesses were performed on an Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector, using a Daicel Chiralpak columns (0.46 cm I.D. × 25 cm) and HPLC grade 2-propanol and *n*-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (NaD line), specific rotation was expressed as deg $cm^3 g^{-1} dm^{-1}$ and concentration as $g cm^{-3}$. Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected.

Materials

Organometallic reactions were carried out under inert gas and under anhydrous conditions. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and used as received avoiding further purification. Organocatalytic reactions were carried out in vials without using inert atmosphere or dried solvents.

Enantioselective α-Alkylation of Aldehydes

General procedure (A): A vial was charged with MacMillan catalyst **11** (0.04 mmol, 8.7 mg), benzoic acid (0.04 mmol, 4.8 mg), acetonitrile (0.5 mL) and water (0.5 mL). The mixture was cooled at 0 °C, and 1,3-benzodithiolylium tetrafluoroborate (0.2 mmol, 48 mg), NaH_2PO_4 (0.2 mmol, 24 mg) and the aldehydes **2a–k** (0.4 mmol) were added.

General procedure (B): A vial was charged with MacMillan catalyst hydrochloride **11**·HCl (0.04 mmol, 10.1 mg), acetonitrile (0.8 mL) and water (0.8 mL). The mixture was cooled at 0 °C, and 1,3-benzodithiolylium tetrafluoroborate (0.2 mmol, 48 mg) and the aldehydes **2a–k** (0.4 mmol) were added. The mixture was stirred for 24 h at the same temperature, the organic solvent was evaporated and the mixture was diluted with Et_2O (3 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 3 mL). The collected organic layers were concentrated under reduce pressure. The residue was diluted in MeOH (1 mL) and $NaBH_4$ (0.8 mmol, 30 mg) was slowly added at 0 °C. After 30 min, the reaction was quenched with water (0.2 mL), the solvent removed under reduced pressure and the residue was extracted with AcOEt (3 × 5 mL). The collected organic layers were dried over Na_2SO_4 and concentrated under reduce pressure.

13a: yield: 98%; 92% *ee*. The desired product was isolated by flash column chromatography (cyclohexane/AcOEt = from 9/1 to 8/2) as a yellow oil; The *ee* was determined by HPLC analysis (Daicel Chiralcel IA column: *n*-hexane/*i*-PrOH 90:10, flow rate 0.50 mL min^{-1}, 30 °C, λ = 232, 254 nm): τ_{major} = 33.3 min, τ_{minor} = 31.2 min; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.26 (m, 5H), 7.21–7.19 (m,1H), 7.13–7.10 (m, 1H), 7.02–6.97 (m, 2H), 5.34 (d, *J* = 9.5 Hz, 1H), 4.08–4.00 (m, 2H), 3.77 (s, 3H), 3.33 (ddd, *J* = 4.9, 6.1, 9.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.1, 137.3, 137.2, 137.1, 130.9, 129.6 (2C), 125.5, 125.4, 122.3, 122.2, 114.1 (2C), 64.4, 56.9, 55.2, 54.0.

Homologation using the Wittig Procedure

Procedure (A): To a solution of aldehydes **12a**, **b**, **e** (0.1 mmol) in THF (1 mL) under nitrogen the Witting reagent (0.25 mmol, 334 mg) was added in one portion. After 20 h the solvent was evaporated.

Procedure (B): To a suspension of NaH (0.15 mmol) in THF (2 mL) a solution of the HWE reagent (0.15 mmol, 30 μL) was slowly added at 0 °C under nitrogen atmosphere. After 1 h a solution of aldehyde **12a** (0.1 mmol) in THF (1 mL) was added. After 20 h the reaction was quenched with water (0.2 mL), the solvent removed under reduced pressure and the residue was extracted with AcOEt (3× 5 mL). The collected organic layers dried over Na_2SO_4 and concentrated under reduced pressure.

Procedure (C): As procedure B at −20 °C using lithium alkoxide prepared from HFIP (0.15 mmol, 15 μL) and *n*-BuLi (0.15 mmol, 2.5 M in THF, 60 μL) in THF (2 mL). The desired product was isolated by flash column chromatography (cyclohexane/AcOEt = from 9/1 to 8/2) as yellow oil. The *ee* was determined by HPLC analysis (see the Supporting Information).

Reductive Removal of Benzodithiol Group; General Procedure

To a solution of **13a–k** (0.19 mmol) in ethanol (1 mL), Raney nickel (0.450 g, slurry in water) was added and the reaction mixture was kept under an H_2 atmosphere (1 atm). After 3 hours the reaction mixture was filtered through a Celite® pad and the organic solvent was removed under reduce pressure. The residue was diluted with AcOEt, the organic layer was separated, and the aqueous layer was extracted with AcOEt (2×5 mL). The collected organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduce pressure. The products were used in the following step without any purification. The enantiomeric excesses of products were not changed during the reaction with Raney nickel.

Preparation of the Iodides 16a–k; General Procedure

To a solution of Ph_3P (200 mg, 0.76 mmol) and 1*H*-imidazole (52 mg, 0.76 mmol) in Et_2O (860 μL) and MeCN (344 μL), I_2 (72.4 mg, 0.57 mmol) was added in portions at room temperature. The resulting suspension was stirred for 1 hour, and **15a–k** (0.19 mmol) in Et_2O (350 μL) was added dropwise. The mixture was stirred for 4.5 h, after which it was diluted with *n*-hexane (5 mL) and the solid was filtered off. The organic solvent was evaporated and the residue. The crude product was purified by flash column chromatography on silica gel using *n*-hexane as eluent.

16a: Yield: 48%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.16–7.12 (m, 2H), 6.90–6.86 (m, 2H), 3.82 (s, 3H), 3.4 (dd, J = 6.1, 9.6 Hz, 1H), 3.31 (dd, J = 8.0, 9.6 Hz, 1H), 3.06–2.97 (m, 1H), 1.41 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.4, 136.4, 127.7 (2C), 113.9 (2C), 55.2, 41.5, 21.6, 15.6.

Preparation of Compounds 17a–e; General Procedure

To a suspension of NaH (60% in mineral oil, 14.4 mg, 0.36 mmol) in DMF (380 μL) dimethyl malonate (41 μL, 41.5 mg, 0.36 mmol) was added dropwise at 0 °C under stirring. After 15 min a solution of iodide **16a–e** (0.09 mmol) in DMF (380 μL) was added and the reaction mixture was allowed to warm to room temperature. After 13 h a saturated solution of NH_4Cl (1 mL) was added and the resulting mixture was extracted with ether (3×6 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel (cyclohexane/AcOEt = from 100/0 to 90/10) to afford **17a–e**.

17a: Yield: 85%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11–7.03 (m, 2H); 6.87–6.83 (m, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.22 (dd, J = 5.8, 9.2 Hz, 1H), 2.25–2.18 (m, 1H), 2.15–2.05 (m, 1H), 2.15–2.05 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 169.8, 158.1, 137.2 (2C), 127.94 (2C), 113.9 (2C), 55.2, 52.4 (2C), 50.0, 37.2, 37.0, 22.6.

Standard Krapcho Procedure for Compounds 17a–e: General Procedure

A mixture of compound **17a–e** (0.07 mmol), LiCl (6 mg, 0.14 mmol) and H_2O (2.5 μL, 0.14 mmol) in dry DMSO was stirred for 13 h at 160 °C. The crude product was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt = 90/10).

18a: Yield: 80%; 92% *ee*; colourless oil. The *ee* was determined by HPLC analysis (Daicel Chiralcel IB column: *n*-hexane/*i*-PrOH 99:1, flow rate 0.50 mL min^{-1}, 30 °C, λ = 214, 254 nm): τ_{major} = 12.6 min, τ_{minor} = 11.5 min; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.12–7.08 (m, 2H), 6.87–6.83 (m, 2H), 3.80 (s, 1H), 3.63 (s, 3H), 2.72–2.62 (m, 1H), 1.25 (d, J = 6.9 Hz, 3H), 2.28–2.13 (m, 2H), 1.97–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.1, 157.9, 138.3, 127.8 (2C), 113.8 (2C), 55.2, 51.4, 38.5, 33.3, 32.3, 22.3; HR-MS: m/z = 222.12563, calcd. for $C_{13}H_{18}O_3$: 222.12559.

Synthesis of 19 and 21

To a solution of *n*-BuLi (2.5 M in hexanes, 192 μL, 0.48 mmol) in THF (200 μL) tributyl(3-methyl-2-butenyl)tin (161 μL, 172 mg, 0.48 mmol) was added dropwise at −78 °C under stirring. The reaction mixture became yellow. After 1 hour iodide **16c** (60 mg, 0.24 mmol) was added and the reaction mixture was stirred at −78 °C for 30 min. Water (1 mL) was added and the resulting mixture was extracted with ether (3×10 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by preparative TLC on silica using hexane as eluent.

19: Yield: 65%; colourless oil; $[\alpha]_D^{20}$: −38.1 (*c* 1.6 in $CHCl_3$), lit:[29] $[\alpha]_D^{20}$: −45.0 (*c* 0.75 in $CHCl_3$); Spectral data are in accord with those in the literature.[29]

21: yield: 21%; colourless oil; $[\alpha]_D^{20}$: −22.4 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.05 (s, 4H), 5.72 (dd, J = 10.3, 17.8 Hz, 1H), 4.87–4.82 (m, 2H), 2.74–2.67 (m, 1H), 2.29 (s, 3H), 1.74 (dd, J = 7.0, 13.8 Hz, 1H), 1.54 (dd, J = 5.2, 13.8 Hz, 1H), 1.17 (d, J = 7.0 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 148.7, 146.5, 134.9, 134.9, 128.9 (2C), 126.9 (2C), 110.0, 51.0, 36.3, 29.7, 28.2, 26.5, 25.4, 21.0; HR-MS: m/z = 202.175223; calcd. for $C_{15}H_{22}$: 202.17215.

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References

[1] a) J. Apsimon, *The Total Synthesis of Natural Products*, Vol. 5, Wiley, New York, **1983**; b) T. Kitahara, Y. Furusho, K. Mori, *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1137.

[2] a) F. Bohlman, M. Lonitz, *Chem. Ber.* **1978**, *111*, 843; b) F. J. McEnroe, W. Fenical, *Tetrahedron* **1978**, *34*, 1661; c) M. Ohno, R. Todoriki, Y. Yamamoto, H. Akita, *Chem. Pharm. Bull.* **1994**, *42*, 1590; d) M. Asaoka, K. Shima, N. Fujii, H. Takei, *Tetrahedron* **1988**, *44*, 4757; e) A. M. S. Mayer, P. B. Jacobson, W. Fenical, R. S. Jacobs, K. B. Glaser, *Life Sci.* **1998**, *62*, 401.

[3] a) C. Fuganti, S. Serra, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3758; b) A. E. Wright, S. A. Pomponi, O. J. McConnell, S. Kohmoto, P. J. McCarthy, *J. Nat. Prod.* **1987**, *50*, 976; c) N. Fusetani, M. Sugano, S. Matsunaga, K. Hashimoto, *Cell. Mol. Life Sci.* **1987**, *43*, 1234.

[4] A. Zhang, T. V. RajanBabu, *Org. Lett.* **2004**, *6*, 1515, and references cited therein.

[5] a) A. I. Meyers, R. K. Smith, *Tetrahedron Lett.* **1979**, *20*, 2749; b) S. Nave, R. P. Sonawane, T. G. Elford, V. K. Aggrawal, *J. Am. Chem. Soc.* **2010**, *132*, 17096; c) C. Fuganti, S. Serra, A. Dulio, *J. Chem. Soc. Perkin Trans. 1* **1999**, 279; d) B. J. Rowe, C. D. Spilling, *J. Org. Chem.* **2003**, *68*, 9502; e) A. Kamal, M. S. Malik, S. Azeeza, S. Bajee, A. A. Shaik, *Tetrahedron: Asymmetry* **2009**, *20*, 1267. For the total synthesis of curcumene see: f) T. Nishimura, Y. Yasuhara, T. Sawano, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7872; g) H. G. Schmalz, C. B. de Koning, D. Bernicke, S. Siegel, A. Pfletschinger, *Angew. Chem.* **1999**, *111*, 1721; *Angew. Chem. Int. Ed.* **1999**, *38*, 1620; h) S. Serra, C. Fuganti, E. Brenna, *Chem. Eur. J.* **2007**, *13*, 6782.

[6] For reviews about organocatalysis, see: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; b) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 4664; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[7] a) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183; b) A. Gualandi, M. G. Emma, J. Giacoboni, L. Mengozzi, P. G. Cozzi, *Synlett* **2013**, *24*, 449.

[8] A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633.

[9] a) S. Afewerki, P. Breistein, K. Pirttilä, L. Deiana, P. Dziedzic, I. Ibrahem, A. Córdova, *Chem. Eur. J.* **2011**, *17*, 8784; b) J. W. Yang, M. T. H. Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110; *Angew. Chem. Int. Ed.* **2005**, *44*, 108; c) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32.

[10] a) P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem.* **2009**, *121*, 1339; *Angew. Chem. Int. Ed.* **2009**, *48*, 1313; b) F. Benfatti, E. Benedetto, P. G. Cozzi, *Chem. Asian J.* **2010**, *5*, 2047; c) M. Guiteras Capdevila, F. Benfatti, L. Zoli, *Chem. Commun.* **2009**, 5919; d) M. Guiteras Capdevila, F. Benfatti, M. Stenta, L. Zoli, *Chem. Eur. J.* **2010**, *16*, 11237; e) R. Sinisi, M. V. Vita, A. Gualandi, E. Emer, P. G. Cozzi, *Chem. Eur. J.* **2011**, *17*, 7404; f) M. Guiteras Capdevila, E. Emer, A. Gualandi, P. G. Cozzi, *ChemCatChem* **2012**, *4*, 968; g) M. Guiteras Capdevila, E. Emer, F. Benfatti, A. Gualandi, C. M. Wilson, P. G. Cozzi, *Asian J. Org. Chem.* **2012**, *1*, 38.

[11] a) L. Zhang, L. Cui, X. Li, S. Luo, J. P. Cheng, *Chem. Eur. J.* **2010**, *16*, 204; b) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685; c) A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286.

[12] J. Vasely, R. Rios, *ChemCatChem* **2012**, *4*, 942.

[13] a) A. Gualandi, E. Emer, M. Guiteras Capdevila, P. G. Cozzi, *Angew. Chem.* **2011**, *123*, 7988; *Angew. Chem. Int. Ed.* **2011**, *50*, 7842; b) A. Gualandi, D. Petruzziello, E. Emer, P. G. Cozzi, *Chem. Commun.* **2012**, *48*, 3614.

[14] a) J. Nakayama, *Synthesis* **1975**, 170; b) J. Nakayama, K. Fujiwara, M. Hoshino, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3567; c) I. Degani, R. Fochi, *Synthesis* **1976**, 759; d) D. Buza, W. Krasuski, *Rocz. Chem.* **1976**, *50*, 2007; e) I. Degani, R. Fochi, *Synthesis* **1977**, 263; f) I. Degani, R. Fochi, *J. Chem. Soc. Perkin Trans. 1* **1978**, 1183; g) I. Degani, R. Fochi, V. Regondi, *Tetrahedron Lett.* **1981**, *22*, 1821.

[15] a) S. Ncube, A. Pelter, K. Smith, *Tetrahedron Lett.* **1976**, *17*, 1983; b) S. Ncube, A. Pelter, K. Smith, P. Blatcher, S. Warren, *Tetrahedron Lett.* **1978**, *19*, 2345; c) C. A. Brown, R. D. Miller, C. M. Lindsay, K. Smith, *Tetrahedron Lett.* **1984**, *25*, 991; d) H. Li, K. Nishiwaki, K. Itami, J. C. Joshida, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1717.

[16] a) M. N. Deshmukh, S. V. Joshi, *Synth. Commun.* **1988**, *18*, 1483; b) Y. Sun, B. Yu, X. Wang, S. Tang, X. She, X. Pan, *J. Org. Chem.* **2010**, *75*, 4224; c) K. Okuyama, Y. Momoi, K. Sugimoto, K. Okano, H. Tokuyama, *Synlett* **2011**, 73; d) D.-J. Chang, H. An, K.-s. Kim, H. H. Kim, J. Jung, J. M. Lee, N.-J. Kim, Y. T. Han, H. Yun, S. Lee, G. Lee, S. Lee, J. S. Lee, J.-H. Cha, J.-H. Park, J. W. Park, S.-C. Lee, S. G. Kim, J. H. Kim, H.-Y. Lee, K.-W. Kim, Y.-G. Suh, *J. Med. Chem.* **2012**, *55*, 10863; e) J. B. Gibbons, K. M. Gligorich, B. E. Welm, R. E. Looper, *Org. Lett.* **2012**, *14*, 4734.

[17] H. Wang, J. R. Denton, H. M. L. Davies, *Org. Lett.* **2011**, *13*, 4316.

[18] a) G. A. Kraus, I. Jeon, *Org. Lett.* **2006**, *8*, 5315; b) Z.-T. Du, S. Zheng, G. Chen, D. Lv, *Molecules* **2011**, *16*, 8053–8061.

[19] D. A. Evans, G. Helmchen, *Asymmetric Synthesis The Essentials*, (Eds.: M. Christmann, S. Bräse), Wiley, Weinheim, **2007**.

[20] J. B. Cumming, P. Kebarle, *J. Am. Chem. Soc.* **1977**, *99*, 5818.

[21] M. F. Landoni, A. Soraci, *Curr. Drug Metab.* **2001**, *2*, 37.

[22] a) A. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260; b) J. S. Harvey, S. P. Simonovich, C. R. Jamison, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 13782; J. Wang, L. Schaeffler, G. He, D. Ma, *Tetrahedron Lett.* **2007**, *48*, 6717.
[23] P. Müller, C. Boléa, *Helv. Chim. Acta* **2002**, *85*, 483.
[24] A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, *Angew. Chem.* **2011**, *123*, 1745; *Angew. Chem. Int. Ed.* **2011**, *50*, 1707.
[25] A. P. Krapcho, *Arkivoc* **2007**, ii, 1.
[26] a) O. Machico, O. Yuuko, H. Kazumi, A. Hiroyuki, *Chem. Phar. Bull.* **2001**, *49*, 1581; b) G. Elford, S. Nave, R. S. Sonawane, W. K. Aggarwal, *J. Am. Chem. Soc.* **2011**, *133*, 16798.
[27] Recently, an interesting organocatalytic approach to bisabolanes was described by Ibrahem and Córdova, by employing a palladium/chiral amine co-catalyzed enantioselective β-arylation of α,β-unsaturated aldehydes; see: I. Ibrahem, G. Ma, S. Afewerki, A. Córdova, *Angew. Chem.* **2013**, *125*, 912; *Angew. Chem. Int. Ed.* **2013**, *52*, 878. (*R*)-Curcumene was obtained in 68% *ee*.
[28] B. H. Lipshutz, R. Crow, S. H. Dimock, E. L. Ellsworth, *J. Am. Chem. Soc.* **1990**, *112*, 4063.
[29] T. Ehara, S. Tanikawa, M. Ono, H. Akita, *Chem. Pharm. Bull.* **2007**, *55*, 1361.

