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Advanced Synthesis & Catalysis

Enantioselective Ammonium Ylide Mediated One-Pot Synthesis of Highly Substituted γ-Butyrolactones

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Abstract: An ammonium ylide mediated access towards *trans*-*β,γ*-disubstituted, *all-trans*-*α,β,γ*-trisubstituted, and *α,α,β,γ*-tetrasubstituted *γ*-butyrolactones bearing a broad variety of functionalities was developed. Starting from widely accessible benzylidene Meldrum's acid derivatives and *α*-bromo carbonyl compounds, *γ*-butyrolactones were obtained in yields between 32–99% with up to excellent diastereoselectivities (>95:5) *via* a DABCO-mediated [2+1] annulation. Utilization of enantiomerically pure cinchona alkaloid derivatives enables the first asymmetric ammonium ylide mediated method to provide (3*R*, 4*R*)-*β,γ*-disubstituted and (2*R*, 3*R*, 4*R*)-*α,β,γ*-trisubstituted *γ*-butyrolactones in moderate to good yields with up to very good enantiomeric ratios (97:3). The scalability of the transformation was proven while determining the absolute configuration.

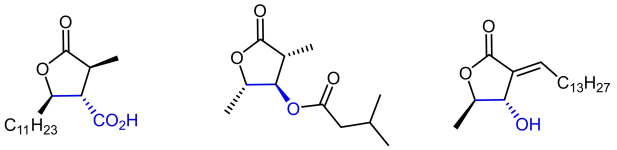
Keywords: asymmetric synthesis; asymmetric catalysis; heterocycles; lactones; multicomponent reactions; ylides.

Introduction

The use of ylides plays an important role in organic synthesis. While phosphorus and sulfur ylides have been exploited extensively in the past,[1] ammonium ylides have attracted considerably less attention. Still, pioneering work of Gaunt *et al.* described ammonium ylides in diastereo- and enantioselective cyclopropanation reactions,[2] and also three- and five-membered heterocycles were synthesized,[3] including aziridines and epoxides,[4] isoxazoline *N*-oxides,[5] pyrazoles,[6] pyrroles,[7] spirocyclic oxindoles[8] and dihydrofurans.[9]

γ-Butyrolactones constitute a valuable structural motif, which is found in a myriad of natural products[10] of which several exhibit interesting biological activities,[11] including antitumor and antibiotic properties (Figure 1).[12]

Based on the demand, a broad variety of synthetic approaches towards *γ*-butyrolactones has been reported to date,[10b,c,13] employing, *e.g.*, transition metal-,[14] organo-[15,14i] or enzyme[16] catalysis. Until now, down-



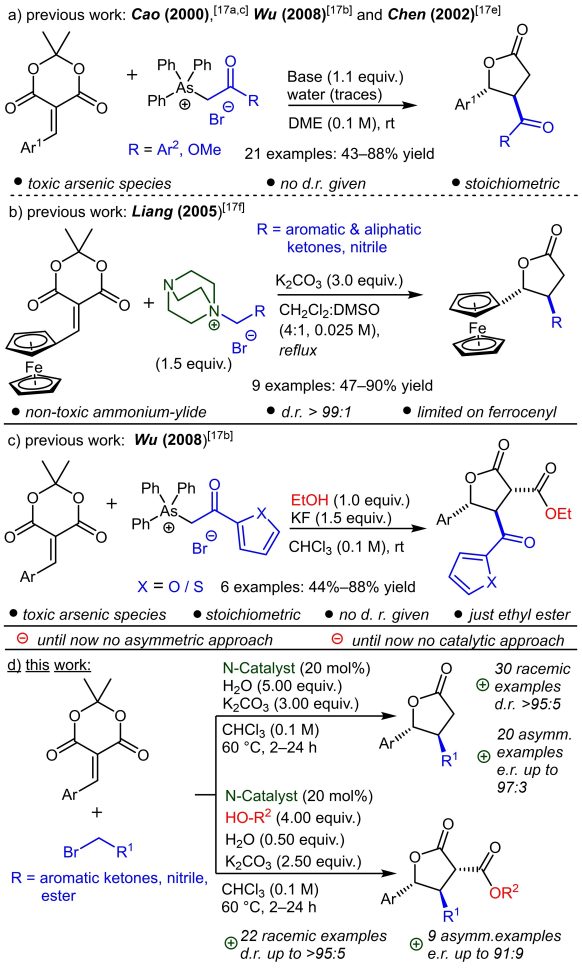
(+)-nephrosteranic acid (+)-blastmycinone (–)-listenolide C1

Figure 1. Selected examples of *trans*-*γ*-butyrolactone-containing natural products.

sides of many methods imply often lavish starting material synthesis or harsh reaction conditions not tolerated by certain functional groups.

Alternative approaches employing "onium ylides" for the synthesis of substituted γ-butyrolactones are published in literature:[17] Cao *et al.* first reported a diastereoselective synthesis of *trans*-β,γ-disubstituted γ-butyrolactones, utilizing stoichiometric amounts of arsonium ylides starting from benzylidene Meldrum's acid derivatives and preformed α-bromo carbonyl arsonium salts.[17a,c] Chen *et al.* broadened the scope of Michael acceptors[17e] and Wu & Cao *et al.* displayed diversity in α-bromo carbonyl donors (Scheme 1a).[17b] Closing it onto analogous nitrogen-based reactions, Liang and co-workers[17f] reported the ammonium ylide mediated method towards *trans*-β,γ-disubstituted γ-butyrolactones. However, this is limited to a sophisticated, yet singularly appearing ferrocenyl substituent within the acceptor system (Scheme 1b). Lastly, the formation of several trisubstituted *all-trans*-γ-butyrolactones again using arsonium ylides was reported by Wu *et al.*[17b] applying a similar method as described previously now employing additional alcohols as nucleophiles (Scheme 1c).

All approaches can be rendered straightforward granting access to densely functionalized molecules from simple starting materials. However, from an ecological and economical point of view, the use of toxic arsenic compounds in stoichiometric amounts for the provision of most given procedures in literature is an addressable issue. The use of non-toxic ammonium ylides as demonstrated by Liang and co-workers reveals a practical solution to the problem, albeit diversity concerning the Michael systems being used may be considered. Ultimately, to the best of our knowledge neither catalytic, nor asymmetric approaches towards *trans*-substituted *y*-butyrolactones using ylides are reported in literature at all. Due to the troublesome toxicity and generally low availability of chiral tertiary arsenic compounds, alternatives prove inevitable for facing the aforementioned challenges. With the abundance of inexpensive non-chiral and chiral tertiary amines such as alkaloids, investigations into a more general, less toxic, catalytic and particularly enantioselective preparation of di- and trisubstituted γ-butyrolactones appeared to be a worthwhile endeavor to us. Furthermore, with the *in situ* preparation of the ammonium salt step-economic issues are served (Scheme 1d).

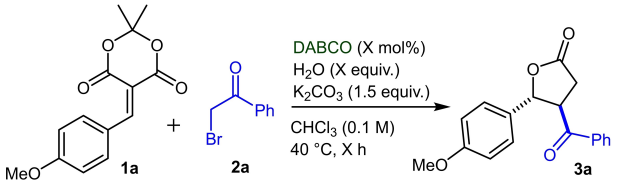


Scheme 1. Ylide-mediated syntheses of γ-butyrolactones.

Results and Discussion

In order to establish an initial catalytic protocol, we examined the diastereoselective reaction of the, *via* Knoevenagel condensation formed,[18] Michael system **1a** and α-bromoacetophenone (**2a**) in the presence of catalytically active DABCO on the basis of literature examples.[17] To our delight, the β,γ-disubstituted γ-butyrolactone **3a** was obtained in 47% yield as single *trans*-diastereoisomer after 24 h. We then set out to optimize the reaction conditions. The results are summarized in Table 1. Since water is essential for the reaction (Table 1, entry 2), we systematically varied the equivalents of water (entries 1–5). The highest conversion was observed with 5.0 equiv. of water. Next, the catalyst loading was varied, which showed an increase in conversion with higher amounts (entries 6–9). Stoichiometric amounts of DABCO did not lead to higher conversions (entries 3 + 10). Further, the reaction time could be shortened to two hours when conducting the reaction at 60 °C instead of 40 °C (21 h) (entries 11–12). 3.0 equiv. of base gave a higher conversion than 1.5 equiv., but a higher loading decreased the conversion (entries 13–14). In order to suppress the formation of byproducts, the amount of **2a** was reduced from 1.5 to 1.1 equiv. (entry 14). When **1a** and **2a** were added in 4 portions over time, the highest conversion (89%) towards γ-butyrolactone

Table 1. Screening of reaction conditions for the catalytic *trans*-*β*,*γ*-disubstituted *γ*-butyrolactone formation.



entry	H_2O (equiv.)	catalyst (mol%)	Time (h)	product[a] (%)
1	2.5	20	24	47
2	–	20	24	–
3	5.0	20	24	56
4	10	20	24	42
5	50	20	24	42
6	5.0	2.5	23	11
7	5.0	5.0	23	17
8	5.0	10	23	26
9	5.0	15	23	37
10	5.0	150	23	44
11[b]	5.0	20	21	52
12[c]	5.0	20	2	42
13[b,c]	5.0	20	2	50
14[b,c,d]	5.0	20	2	66
15[b,c,d,e]	5.0	20	2	89

All reactions were conducted on a 0.1 mmol scale.
[a] Quantification *via* ^{1}H NMR spectroscopy with DMF as an internal standard.
[b] Reaction conducted with 3.0 equiv. base.
[c] Reaction conducted at 60 °C.
[d] Reaction conducted with 1.1 equiv. **2a**.
[e] **1a** and **2a** were added in portions, see SI for details.

3a was observed after 2 h, which we used in further reactions (entry 15).

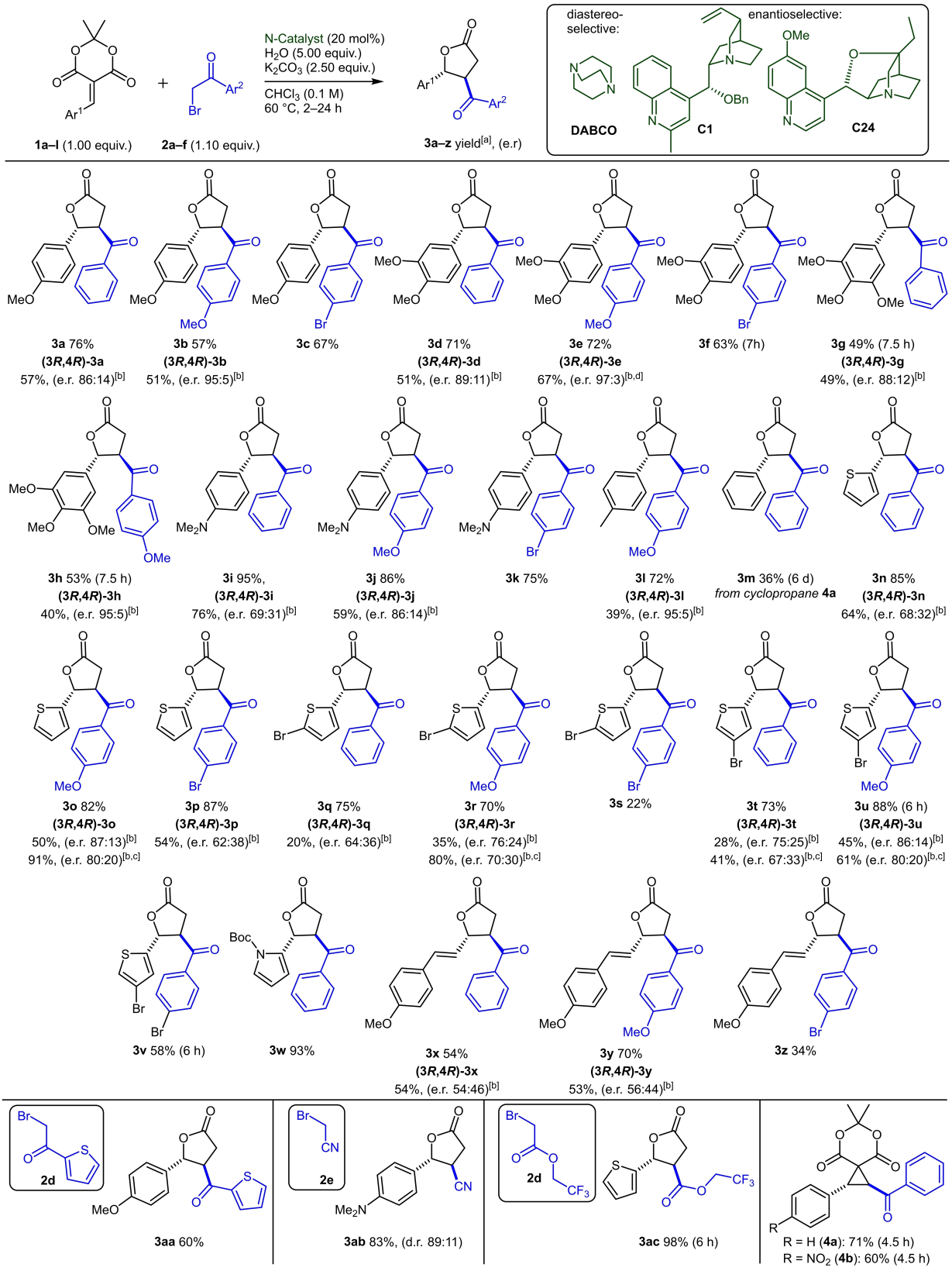
With these optimized reaction conditions in hand, we turned our attention towards the scope of the method (Scheme 2). 11 Michael systems **1a–k** containing different substituents, including heteronuclear and vinylogous aromatic systems were converted in good to excellent yields. The *trans*-diastereomers (d.r. > 95:5) were formed exclusively, as identified *via* the corresponding ^{1}H NMR spectra in comparison with the literature known *trans*-*γ*-butyrolactone **3aa**.[19] The electron poor Michael systems **1f** and **1l** remained on the level of cyclopropanes, as their formation can be reasoned by the proposed catalytic cycle (*vide infra*, Scheme 4). However, the phenyl-substituted cyclopropane **4a** could be converted to the corresponding *γ*-butyrolactone **3m** after elongated reaction times (6 days). Hydrolysis of Michael systems **1** might explain the diminished yields for some examples upon prolonged reaction time. Signals in the corresponding crude ^{1}H NMR spectra indicate the presence of free aldehyde to a greater or lesser extent, which led to the formation of various byproducts.

For the cases tested, *α*-bromoacetophenone (**2a**) could successfully be replaced by substituted 4-methoxy- (**2b**) and 4-bromo-*α*-bromoacetophenone (**2c**), or 2-(2-bromoacetyl) thiophene (**2d**)[20] leading to the desired products **3a–aa** in comparable yields and without loss of any diastereoselectivity (Scheme 2). Furthermore, an access to nitrile **3ab** and ester functionalized *γ*-butyrolactones **3ac** was enabled by the use of bromoacetonitrile (**2e**) or 2,2,2-trifluoroethyl bromoacetate (**2f**) as donors (Scheme 2) or by Baeyer-Villiger oxidation of lactone **3o** to ester **3ad** in a subsequent reaction (Scheme 3).

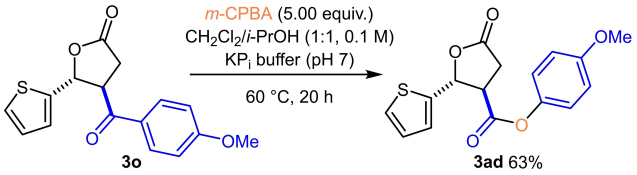
Mechanistically, we assume in accordance to known reports,[17] alkylation of the tertiary amine **C** (diastereoselective: DABCO, enantioselective: cinchona alkaloid derivative) with *α*-bromo carbonyl compound **2**, to form the ammonium salt **I** *in situ*. After deprotonation to ylide **II**, it attacks the Michael acceptor **1**, which undergoes a cyclopropanation in a [2 + 1] annulation as the key step of this approach. *Trans*-substituted cyclopropanes **4** with an electron-rich Ar^1-substituent exhibit a donor-acceptor character.[21] This leads to a Cloke-Wilson rearrangement[22] *via* the stabilized carbocation **IV** under liberation of acetone and decarboxylation to yield the *β*,*γ*-disubstituted *γ*-butyrolactone **3**. Electron-withdrawing Ar^1-substituents led to stable cyclopropanes **4**, since the formation of carbocation **IV** is not favorable (Scheme 4).[17b]

Due to the broad occurrence of *γ*-butyrolactone moieties bearing configurationally defined substituents in natural products, the approach was extended towards the first enantioselective catalytic "onium" ylide mediated method. Based on our previous work[9e] we applied cinchona alkaloid-derivatives as chiral catalysts. After screening of 34 catalysts[2c,8,9e,23] with the electron-rich Michael acceptor **1g** and 4-methoxy-*α*-bromoacetophenone (**2b**) (Scheme 5), we established a protocol obtaining good yields and up to excellent enantiomeric ratios using adapted conditions with longer reaction times as in the DABCO catalyzed approaches. While the naturally occurring cinchona alkaloids showed no conversion, we varied several substituents on the chinolin-system and introduced sterically demanding protecting groups for the hydroxy- and amine-functionalities. The *O*-benzyl-protected and 2′-methylated cinchonidine-derivative **C1**, which we recently employed in the enantioselective formation of dihydrofurans,[9e] gave the best results regarding yield and enantiomeric excess. Noteworthy, applying *β*-isoquinidine (**C23**) the opposite *trans*-enantiomer was obtained with a moderate enantiomeric ratio of 39:61.

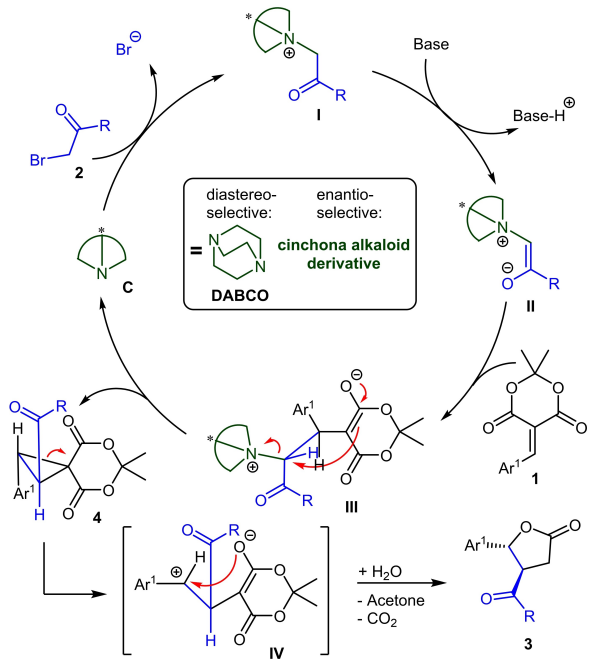
Subsequently, **C1** was applied to examine the scope of asymmetric *β*,*γ*-disubstituted *γ*-butyrolactone formation (Scheme 2). The best enantiomeric ratio of 97:3 was obtained for the reaction with the 3,4-OMe-



Scheme 2. Scope of the *trans-β,γ*-disubstituted γ-butyrolactone **3** synthesis. Diastereoselective reactions were conducted on a 0.25 mmol scale, all d.r. > 95:5. Michael system **1** and donor **2** were added in 4 portions. For the enantioselective transformation, **C1** was employed (e.r. determined by HPLC utilizing chiral stationary phases). [a] Yield of isolated product. [b] 0.10 mmol scale. [c] Reaction was catalyzed with **C24** (2 h). [d] 1.0 mmol scale.



Scheme 3. Baeyer-Villiger oxidation of γ-butyrolactone **3 o**.



Scheme 4. Proposed mechanism of lactone formation.

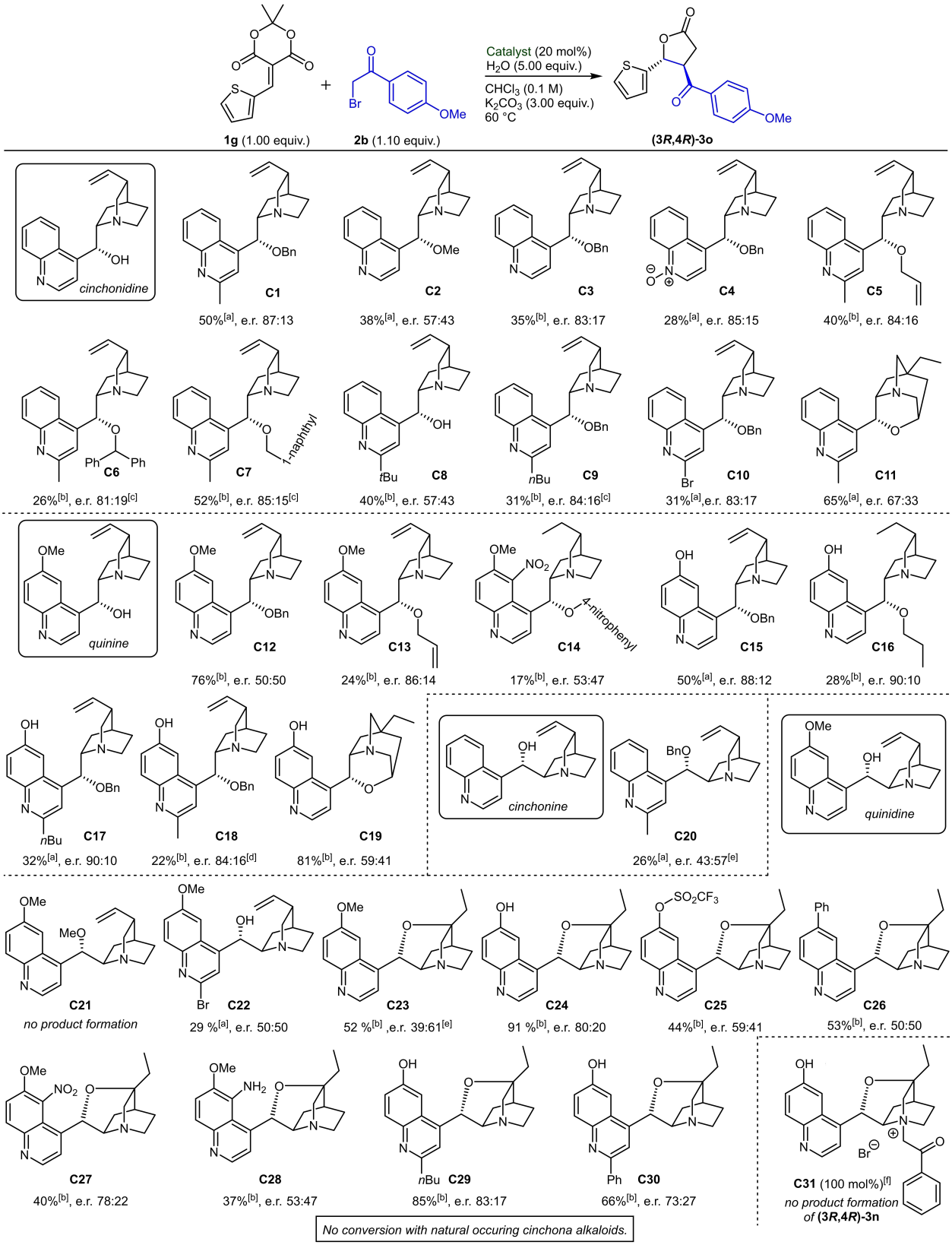
disubstituted Michael system **1 b** and 4-methoxy-α-bromoacetophenone (**2 b**). For the substituted styrene system **1 k** the enantioselectivity was decreased, which can be attributed to the higher flexibility of the substituent. In general, a more electron donating character of used acceptors led to higher enantioselectivities and mostly better yields. Lower yields compared to the racemic approach might be attributed to longer reaction times at 60 °C leading to partial decomposition of γ-butyrolactones and the Michael acceptor (*vide supra*). In order to avoid product degradation under these reaction conditions over time and to obtain higher yields, β-isocupreidine (**C24**) was used, which led to a dramatic shortening of the reaction time (2 h), albeit the products were obtained with a slightly reduced e.r. This rate enhancement may be explained by the high nucleophilicity of the tertiary amine, due to the reduced steric hindrance reported by Hatakeyama *et al.*[23i] However, the usage of stoichiometric amounts of the derivative preformed chiral ammonium salt **C31** did not led to any formation of γ-butyrolactone **3 n** (Scheme 5). This is consistent with the result of lower product formation using stoichiometric amounts of DABCO as indicated in the screening for reaction conditions (Table 1). Therefore, further investigations were only performed in a catalytic mode.

To test the general applicability of this asymmetric method, we additionally demonstrated the scalability of Michael system **1 g** with donor **2 b** on a 3.0 mmol scale, which provided almost the identical yield (46%, compared to 50%) and stable enantioselectivity (86:14, compared to 87:13). The absolute configuration of isolated γ-butyrolactones was identified as (3*R*, 4*R*) *via* chemical correlation with the optical rotary power of the known carboxylic acid (**3*S***, **4*S***)-**3 af**.[24] Therefore, lactone **3 e** was oxidized under Baeyer-Villiger conditions to ester (**3*R***, **4*R***)-**3 ae** and was subsequently hydrolyzed providing γ-butyrolactone **3 af** (Scheme 6). The measured optical rotary power of $[\alpha]_D^{25}+29.8$ (c 1.0, MeOH) proved the (**3*R***, **4*R***) configuration {literature value for lactone (**3*S***, **4*S***)-**3 af**: $[\alpha]_D^{25}$–29.4 (c 1.0, MeOH)}.[24]

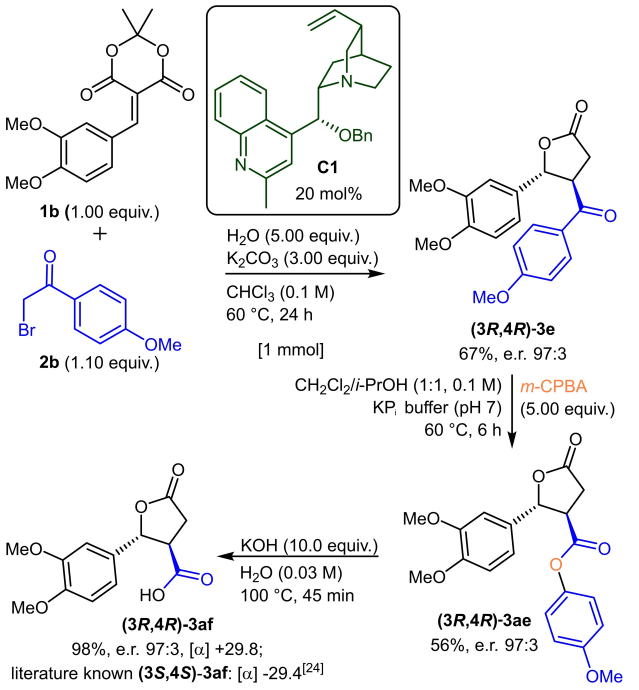
Altogether, we transferred our new method to the first asymmetric "onium" ylide mediated formation of (3*R*, 4*R*)-β,γ-disubstituted γ-butyrolactones. The scope was demonstrated by synthesizing 20 enantiomerically enriched γ-butyrolactones. It was shown that mostly electron-rich donors and acceptors led to high enantioselectivities in up to good yields.

Harnessing the full potential of our approach, we turned our attention to the synthesis of *all-trans*-α,β,γ-trisubstituted γ-butyrolactones **5**. According to the catalytic cycle proposed, the presence of an alcohol should alter the course of the reaction. Ultimately, decarboxylation in the last step would be prevented by the formation of an ester following the cleavage of the intermediate cyclopropane (Table 2, Scheme 7).[17b] After a screening for adapted reaction conditions, we found that lowering the amount of water to 0.50 equiv., addition of 4.00 equiv. *tert*-butyl alcohol (**6 a**), heating at 60 °C and 2 h reaction time resulted in the highest conversion (Table 2, entry 5).

Having the conditions optimized, we again turned our focus on the scope of the method (Scheme 7). Several different *trans*-α,β,γ-trisubstituted γ-butyrolactones containing aromatic and heteroaromatic moieties were isolated in moderate to excellent yields of up to 92% and good to excellent diastereomeric ratios of up to >95:5. In general, acceptor systems with higher electron density led to excellent diastereomeric ratios of the isolated product, whereas heteronuclear aromatic substituents enabled higher yields with a small decrease in diastereoselectivity. Beside *tert*-butyl alcohol (**6 a**), we showed that ethyl (**6 b**), benzyl (**6 c**), allyl (**6 d**), isopropyl (**6 e**), and 2-furfuryl alcohol (**6 f**) were accepted in the reaction with Michael system **1 a** and α-bromoacetophenone (**2 a**) leading to moderate to good yields and good to excellent diastereoselectivities. In general, higher yields were obtained using

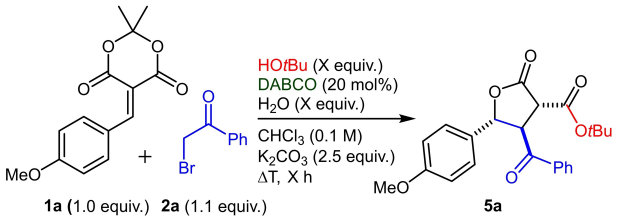


Scheme 5. Enantioselective screening of catalysts **C**. All reactions were carried out on a 0.10 mmol scale. [a] Yield of isolated product. [b] Quantification via ^{1}H NMR spectroscopy with DMF as an internal standard. [c] Product obtained with d.r. 3:1 (*trans:cis*). [d] 8.0 mol% catalyst loading. [e] Opposite *trans*-enantiomer favored. [f] No more *α*-bromoacetophenone (**2a**) was added.



Scheme 6. Determination of the absolute configuration of lactone (**3*R***, **4*R***)-**3e** *via* chemical correlation.

Table 2. Screening of reaction conditions towards *all-trans-α,β,γ*-substituted *γ*-butyrolactones **5**.



entry	HO*t*Bu (equiv.)	H_2O (equiv.)	temp. (°C)	time (h)	product[a] (%)
1	4	1	25	22	50
2	4	1	40	2	55
3	4	1	60	2	65
4	4	0.5	40	4	60
5	4	0.5	60	2	71
6	2	1	40	4	48
7	2	1	60	4	65

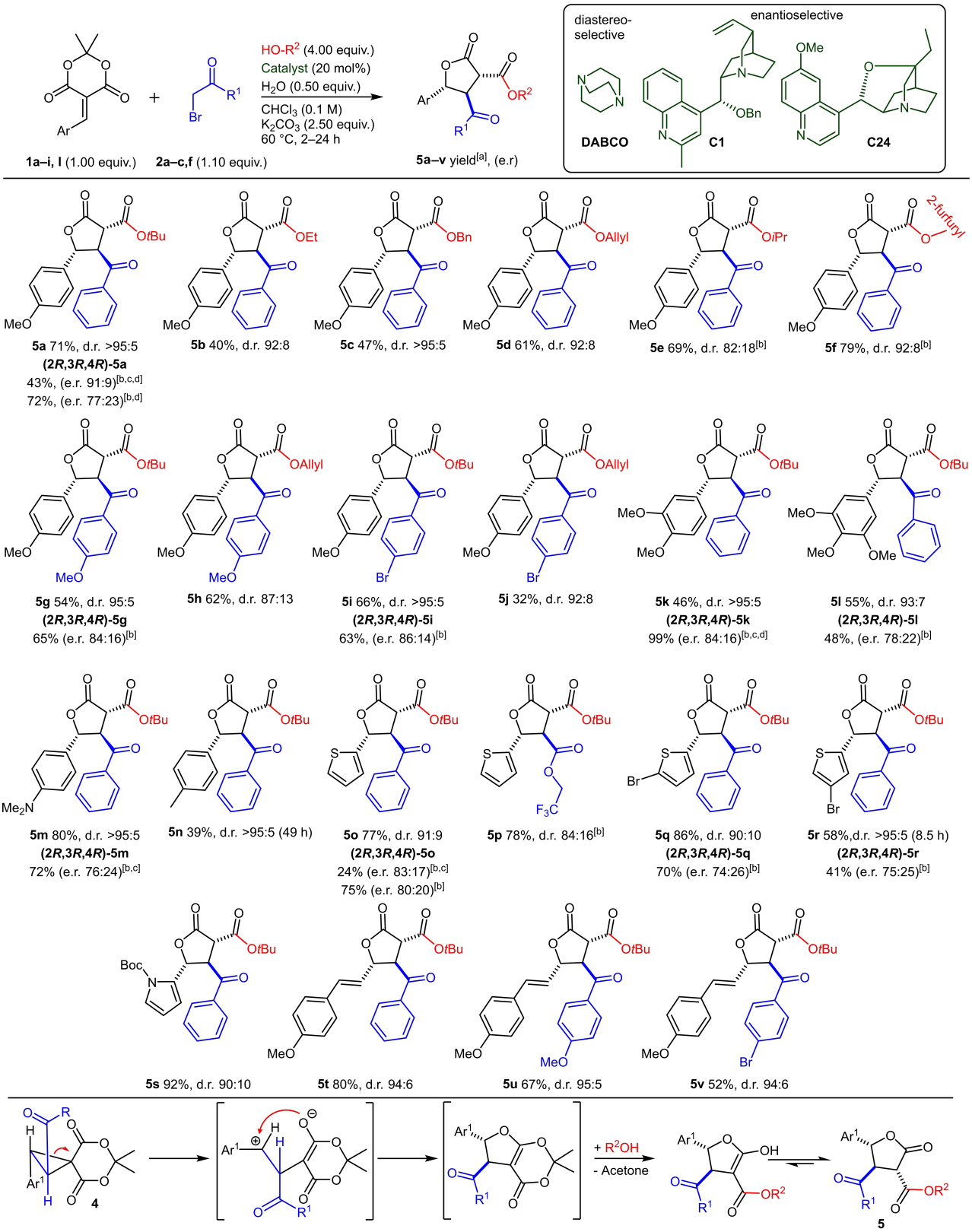
All reactions performed on a 0.25 mmol scale.
[a] Product formation was determined by ^{1}H NMR spectroscopy using DMF as an internal standard.

alcohols, which provided more base-stable esters. To test other donors **2**, we examined the reaction of 4-methoxy (**2b**), 4-bromo *α*-bromoacetophenone (**2c**), and 2,2,2-trifluoroethyl bromoacetate (**2f**) with different Michael systems and alcohols. To our delight, all reactions yielded the desired products in good to excellent diastereomeric ratios. The *all-trans*-relative configuration of *α,β,γ*-trisubstituted *γ*-butyrolactones was determined by comparison of the coupling constants from ^{1}H NMR spectroscopic evidence of literature-known examples with X-ray-data.[17b,25]

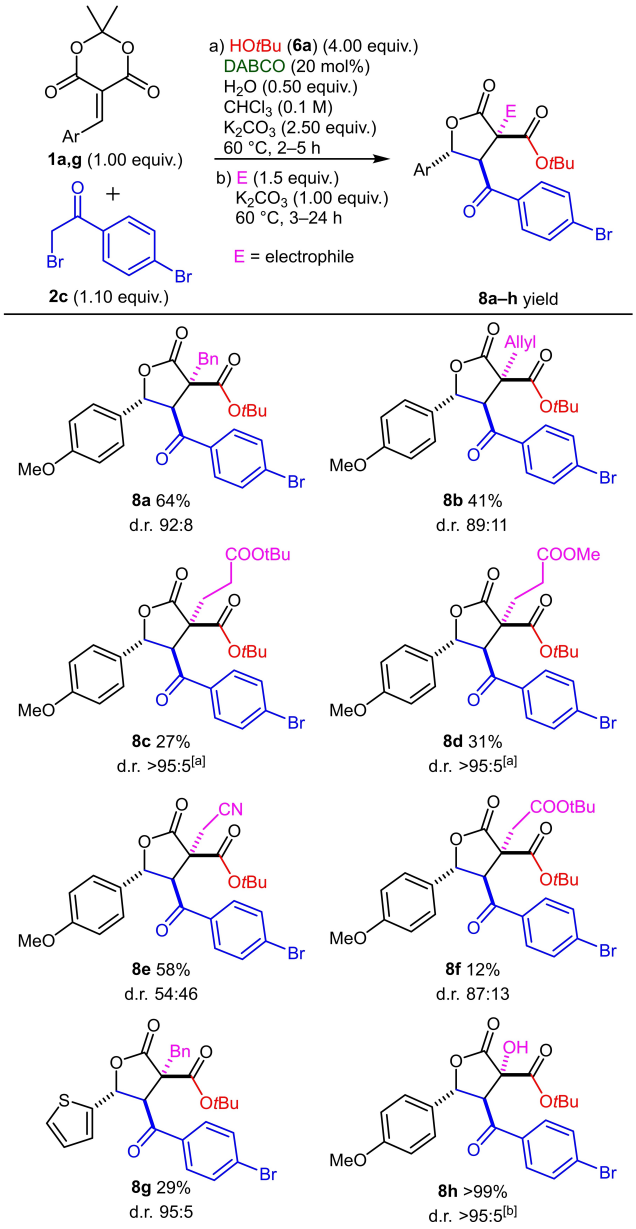
Overall, we developed an effective synthetic route towards 22 all-*trans*-*α,β,γ*-trisubstituted *γ*-butyrolactones in an attractive multicomponent reaction (MCR) using cheap and extensively available starting materials with DABCO as catalyst. To illustrate the synthetic usability and scalability of this method we performed the reaction of Michael system **1a** with 4-bromo *α*-bromoacetophenone (**2c**) and *tert*-butyl alcohol (**6a**) on a 3.00 mmol scale obtaining a slightly decreased yield (54%, compared to 66%) and diastereomeric ratio (93:7, compared to >95:5) in comparison to the 0.25 mmol scale reactions. Furthermore, application of the enantioselective version utilizing **C1** and **C24** for selected examples provided 9 enantiomerically enriched (2*R*,3*R*,4*R*)-*α,β,γ*-trisubstituted *γ*-butyrolactones: Almost quantitative yield (99%) was obtained for the trisubstituted lactone (**2*R***, **3*R***, **4*R***)-**5k** whereas the 4-methoxy- and phenyl-substituted product (**2*R***, **3*R***, **4*R***)-**5a** showed best enantioselectivity (91:9). In general, the use of *β*-isocupreidine (**C24**) led to higher yields with a simultaneous decrease of the enantiomeric ratio compared to catalyst **C1**, due to shorter reaction times with thus less hydrolysis and decarboxylation of the ester. (Scheme 7).

Conclusions

In summary, a highly diastereoselective method applying DABCO-derived ammonium ylides in a one-pot synthesis of *trans-β,γ*-disubstituted and *all-trans-α,β,γ*-trisubstituted *γ*-butyrolactones was developed. *Via* cinchona-derivative catalysis, the extension to the first catalytic, enantioselective *γ*-butyrolactone synthesis using ammonium ylides was successfully established. Obviously, even higher substituted lactones can be readily obtained: Inspired by the work reported in literature,[14f,26] we were confident that highly diastereoselective *α*-derivatisation should be feasible in an one-pot-approach. Preliminary experiments with Michael system **1a** and 4-bromo-*α*-bromoacetophenone (**2c**), and various electrophiles **7**[27] proved the assumption as correct (Scheme 8). Furthermore, also *α*-hydroxyl substituted *γ*-butyrolactone **8h** was obtained in quantitative yield when starting from lactone **5i** after only 10 minutes.[28] So finally, also tetrasubstituted *γ*-butyrolactones bearing a quaternary stereogenic center are accessible, thus further demonstrating the power of the initial MCR.



Scheme 7. Above) Scope of the *all-trans-α,β,γ*-substituted *γ*-butyrolactone **5** synthesis. Diastereoselective reactions were conducted on a 0.25 mmol scale. For the enantioselective transformation, **C24** was employed. [a] Yield of isolated product. [b] Reaction was carried out on a 0.10 mmol scale. [c] Reaction was catalyzed with **C1**. [d] e.r. determined after decarboxylation of malonic ester. Below) Proposed mechanism of *α,β,γ*-substituted butyrolactone **5** formation.



Scheme 8. One-pot MCR towards tetrasubstituted γ-butyrolactones. [a] Reaction carried out with no additional base and by adding DMF in b) at 40 °C. [b] Not a one-pot-synthesis: reaction started from **5i** on 0.1 mmol scale.

Experimental Section

General Experimental Considerations

All used chemicals were purchased from *TCI International*, *Sigma-Aldrich/Fluka*, *VWR International/Merck* and *Alfa Aesar*. Pure solvents were either purchased or distilled prior to use. Dry solvents were either taken from a *MBraun* drying machine (modelMB SPS-800) or distilled over CaH_2 or NaK alloy. Reactions under inert conditions were performed using standard *Schlenk*-technique under dry Ar/N_2 atmosphere with magnetic stirring. NMR spectra were recorded on a *Bruker Advance DRX/600* spectrometer. ^1H NMR analysis were admitted at 600 MHz and ^{13}C NMR analysis were measured proton decoupled at 151 MHz. Chemical shifts are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR; MeOD-d_4: 4.87 ppm for ^1H NMR and 49.00 ppm for ^{13}C NMR). The multiplicity in NMR spectra is given in the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and its combinations. High resolution mass spectra were recorded on *Thermo Fisher Scientifics* (FT-ICR-MS) *LTQ FT Ultra* using electrospray ionization (ESI^+) at *ZEA3* of *Forschungzentrum Jülich GmbH* or on *Brukers UHR-QTOF maXis 4G* at *Heinrich Heine University Düsseldorf*. Analytical thin layer chromatography was performed by using silica gel interlayer (*Macherey-Nagel POLYGRAM® SIL G/UV254*) and visualized by UV irradiation or $KMnO_4$ solution. Enantiomeric ratios were measured on a *Dionex Gynkotek* HPLC using columns from *Daicel* and *Phenomenex* applying heptane:2-propanol mixtures with 0.5 mL/min flow rate (used columns indicated at respective products in SI). Flash column chromatography was performed with silica gel (*Macherey-Nagel, 0.040–0.063 mm, 230–400 mesh*). Optical rotations were measured on an *A.Krüss Optronic P8000* polarimeter in a 1 dm measuring cell at $\lambda =$ 589 nm. Melting points were measured on a *Büchi Melting Point B 540* device with a heating rate of 1 °C/min.

All syntheses of Michael systems **1**, cyclopropanes **4**, catalysts **C**, β,γ-disubstituted **3**, α,β,γ-trisubstituted **5** and α,α,β,γ-tetrasubstituted γ-butyrolactones **8** are described and analytically characterized in the Supporting Information.

General Procedure for the Synthesis of Michael Systems (GP1).

Aldehyde (10.0 mmol, 1.00 equiv.) and Meldrum's acid (12.0 mmol, 1.20 equiv.) were suspended in water (3.0 mL) and heated up to 75 °C. The reaction mixture was stirred until the condensation was completed. After full conversion, the reaction was cooled to ambient temperature, the product precipitated, was filtered *via* a glass funnel and dried under reduced pressure to yield the desired Michael system **1**.

General Procedure for the Synthesis of Michael Systems (GP2).

Meldrum's acid (12.0 mmol, 1.20 equiv.) was dissolved in CH_3CN (10 mL), then aldehyde (10.0 mmol, 1.00 equiv.) and piperidine (50 µL, 5 mol%) were added. The reaction was stirred until the condensation was completed. The solvent was evaporated to give the desired product **1**.

General Procedure for the Synthesis of Racemic *trans*-β,γ-disubstituted γ-butyrolactones (GP3).

K_2CO_3 (103.7 mg, 0.75 mmol, 3.00 equiv.) and DABCO (5.6 mg, 0.05 mmol, 20 mol%) were dissolved in $CHCl_3$ (2.5 mL). DMF (19,2 µL, 0.25 mmol, 1.00 equiv., internal standard) and water (22.5 µL, 1.25 mmol, 5.00 equiv.) were added to the reaction mixture. Michael system **1** (0.25 mmol, 1.00 equiv.) and bromo donor **2** (0.275 mmol, 1.10 equiv.) were divided into 4 portions which were added each to the reaction mixture in intervals of 15 min. The reaction was stirred at 60 °C for 2 h. After full conversion of the starting materials the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 25 mL). The crude mixture was

purified by flash column chromatography to obtain the *trans-β,γ*-disubstituted *γ*-butyrolactone **3**.

General Procedure for the Synthesis of Enantiomerically Enriched (3*R*, 4*R*)-*β,γ*-disubstituted *γ*-butyrolactones (GP4).

K_2CO_3 (41.5 mg, 0.30 mmol, 3.00 equiv.) and 9-O-benzyl-2'-methyl-cinchonidine (**C1**) (8.0 mg, 0.02 mmol, 20 mol%) were dissolved in $CHCl_3$ (1.0 mL). DMF (7.7 µL, 0.10 mmol, 1.00 equiv., internal standard) and water (9 µL, 0.50 mmol, 5.00 equiv.) were added to the reaction mixture. Michael system **1** (0.10 mmol, 1.00 equiv.) and bromo donor **2** (0.11 mmol, 1.10 equiv.) were divided into 4 portions which were added each to the reaction mixture in intervals of 3 h. The reaction was stirred at 60 °C and the reaction was completed after 24 h, quenched saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 25 mL). The crude mixture was purified by flash column chromatography to obtain the (3*R*, 4*R*)-*β,γ*-disubstituted *γ*-butyrolactone **3**.

General Procedure for the Synthesis of Racemic *all-trans-α,β,γ*-trisubstituted *γ*-butyrolactones (GP5).

Michael system **1** (0.25 mmol, 1.00 equiv.), bromo donor **2** (0.275 mmol, 1.10 equiv.), K_2CO_3 (86.4 mg, 0.625 mmol, 2.50 equiv.) and DABCO (5.6 mg, 0.05 mmol, 20 mol%) were dissolved in $CHCl_3$ (2.5 mL). DMF (19.2 µL, 0.25 mmol, 1.00 equiv., internal standard), water (2.25 µL, 125 µmol, 0.50 equiv.) and alcohol **6** (1.00 mmol, 4.00 equiv.) were added to the reaction mixture. The reaction was stirred at 60 °C and after 2–5 h the reaction was completed, quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 25 mL). The crude mixture was purified by flash column chromatography to obtain the *all-trans α,β,γ*-trisubstituted *γ*-butyrolactone **5**.

General Procedure for the Synthesis of Enantiomerically Enriched (*2R, 3R, 4R*) *α,β,γ*-trisubstituted *γ*-butyrolactone (GP6).

Michael system **1** (0.10 mmol, 1.00 equiv.), bromo donor **2** (0.11 mmol, 1.10 equiv.), K_2CO_3 (34.6 mg, 0.25 mmol, 2.50 equiv.) and *β*-ICD (**C24**) (6.2 mg, 0.02 mmol, 20 mol%) were dissolved in $CHCl_3$ (1.0 mL). DMF (7,7 µL, 0.10 mmol, 1.00 equiv., internal standard), water (1 µL 0.05 mmol, 0.50 equiv.) and alcohol **6** (1.00 mmol, 4.00 equiv.) were added to the reaction mixture. The reaction was stirred at 60 °C and after 2–7 h the reaction was completed, quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 25 mL). The crude mixture was purified by flash column chromatography to obtain the (2*R*, 3*R*, 4*R*) *α,β,γ*-trisubstituted *γ*-butyrolactone **5**.

General Procedure for the Synthesis of Racemic *α,α,β,γ*-tetra-substituted *γ*-butyrolactone (GP7).

Michael system **1** (0.25 mmol, 1.00 equiv.), bromo donor **2** (0.275 mmol, 1.10 equiv.), K_2CO_3 (86.4 mg, 0.625 mmol, 2.50 equiv.) and DABCO (5.6 mg, 0.05 mmol, 20 mol%) were dissolved in $CHCl_3$ (2.5 mL). DMF (19.2 µL, 0.25 mmol, 1.00 equiv., internal standard), water (2.25 µL, 125 µmol, 0.50 equiv.) and alcohol **6** (1.00 mmol, 4.00 equiv.) were added to the reaction mixture. The reaction stirred at 60 °C. After 2–5 h the reaction was completely converted to trisubstituted *γ*-lactone **5**, K_2CO_3 (34.6 mg, 0.25 mmol, 1.00 equiv.) and electrophile **7** (0.38 mmol, 1.50 equiv.) were added to the reaction mixture. When product formation was completed, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 25 mL). The crude mixture was purified by flash column chromatography to obtain the *α,α,β,γ*-tetrasubstituted *γ*-butyrolactone **8**.

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[28] Consecutive reaction by addition of *m*-CPBA after lactone formation leads to a 1:1 mixture of the desired product and an uncharacterized side product.

