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Organocatalyzed Asymmetric Allylic Alkylation Enables Synthesis of Chiral γ-Lactones Bearing Vicinal Tertiary and Quaternary Stereocenters

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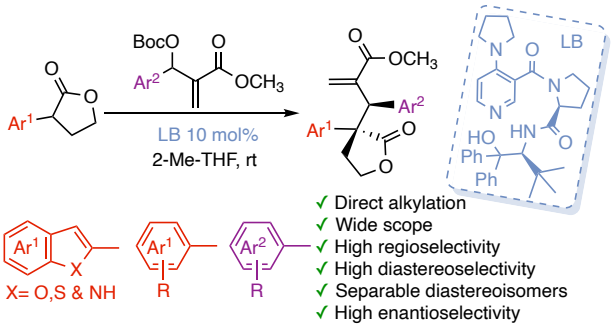
Supporting Information Placeholder

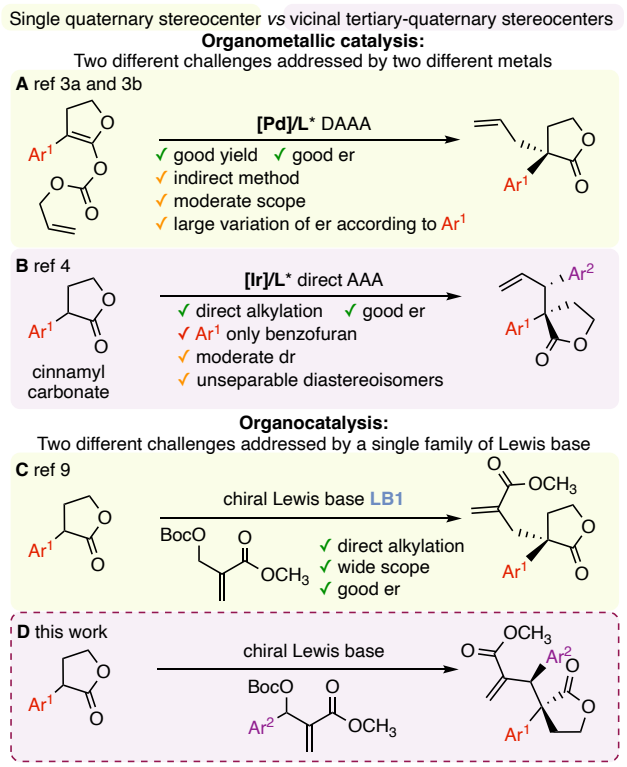


ABSTRACT: The synthesis of enantioenriched α-aryl-α'-allyl-γ-butyrolactones bearing vicinal tertiary and quaternary stereocenters through organocatalyzed asymmetric allylic alkylation is reported. The process demonstrated that weakly stabilized enolates derived from α-aryl-γ-butyrolactones can undergo regio-, diastereo- and enantioselective allylation using the proper activation of Morita–Baylis–Hillman (MBH) carbonates.

Investigation of catalytic asymmetric construction of stereocenters requires both the discovery of activation modes and the demonstration of their applicability to compounds exhibiting great structural diversity. It is well recognized that the second achievement can be highly challenging when the construction of quaternary stereocenters (i.e. carbon atoms bearing four different carbon substituents) is envisaged.[1] Asymmetric allylic alkylations (AAAs) are among the most popular processes for the construction of quaternary stereocenters.[2] Continuous progress in AAA was made by the design of catalysts and ligands with the fittest stereoelectronic properties to improve stereoinduction. Nevertheless, this process often entails the emergence of over-represented classes of precursors of stabilized enolates (e.g. dicarbonyl compounds, α-aryloxoindole or even benzofuran-2(3H)-one). Exploration of the reactivity of uncommon classes of compounds is consequently highly desirable. α-Aryl-γ-butyrolactones embedded synthetic useful features in both the lactone function and the structural diversity available to the aryl moiety. Despite their easy availability, their usefulness in AAA was addressed only recently. Metal-mediated catalysis was first described. Palladium catalyzed decarboxylative asymmetric allylic alkylation (DAAA), whichs avoid the use of strong stoichiometric base, proved to be efficient for the construction of enantioenriched α-aryl-α'-allyl-γ-butyrolactones containing a single stereocenter (Scheme 1, A).[3] Unfortunately, high enantiomeric ratios were found for lactones bearing hindered aryl groups. At the same time the synthesis of enantioenriched lactones bearing adjacent quaternary and tertiary stereocenters was achieved[4] through the use of iridium catalysis[5] (Scheme 1, B). Nonetheless, the broad applicability of this strategy has not been demonstrated to date. As frequently observed in the last two decades organocatalysis is a fruitful complementary approach to organometallic catalysis. Organocatalyzed AAA, mediated by the Lewis base activation of Morita–Baylis–Hillman (MBH) adducts,[6] to access single quaternary stereocenter[7] or adjacent quaternary and tertiary stereocenters,[8] mainly involved stabilized prochiral nucleophiles. However, recently, the synthesis of γ-butyrolactones bearing a single quaternary stereocenter by organocatalyzed AAA has been shown to be possible through the design of a specific class of Lewis base (LB) (Scheme 1, C).[9] This demonstrates that **LB1** was able to control the addition of the prochiral faces of the lactone enolate on the chiral allyl-pyridinium intermediate by non-covalent interactions. The access to chiral γ-butyrolactones bearing adjacent tertiary and quaternary stereocenters requires additional levels of control which is well illustrated by the need of two different metals (Pd *vs* Ir) in metal catalyzed AAA. In the present work, we use such Lewis base to catalyze AAA of the less studied α-

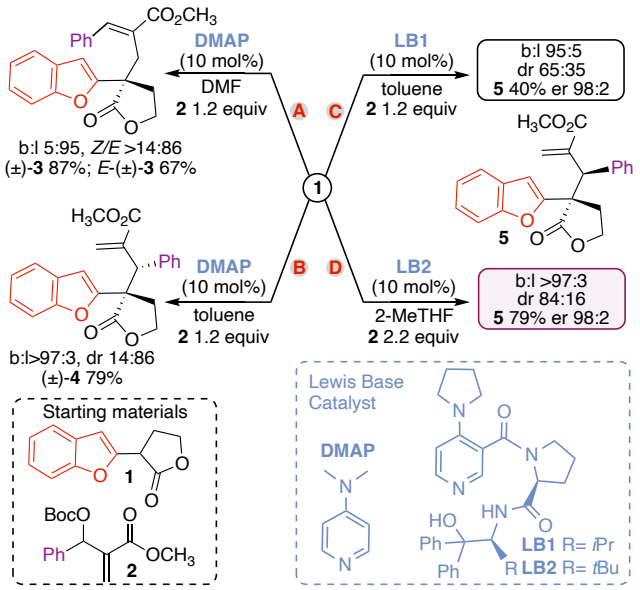
aryl-γ-butyrolactones scaffold and efficiently fix selectivity issues (i.e. regio-, diastereo-, and enantioselectivities) required for the construction of adjacent tertiary and quaternary stereocenters (scheme 1, D).

Scheme 1. Access to α-aryl-α'-allyl-γ-butyrolactones using AAA



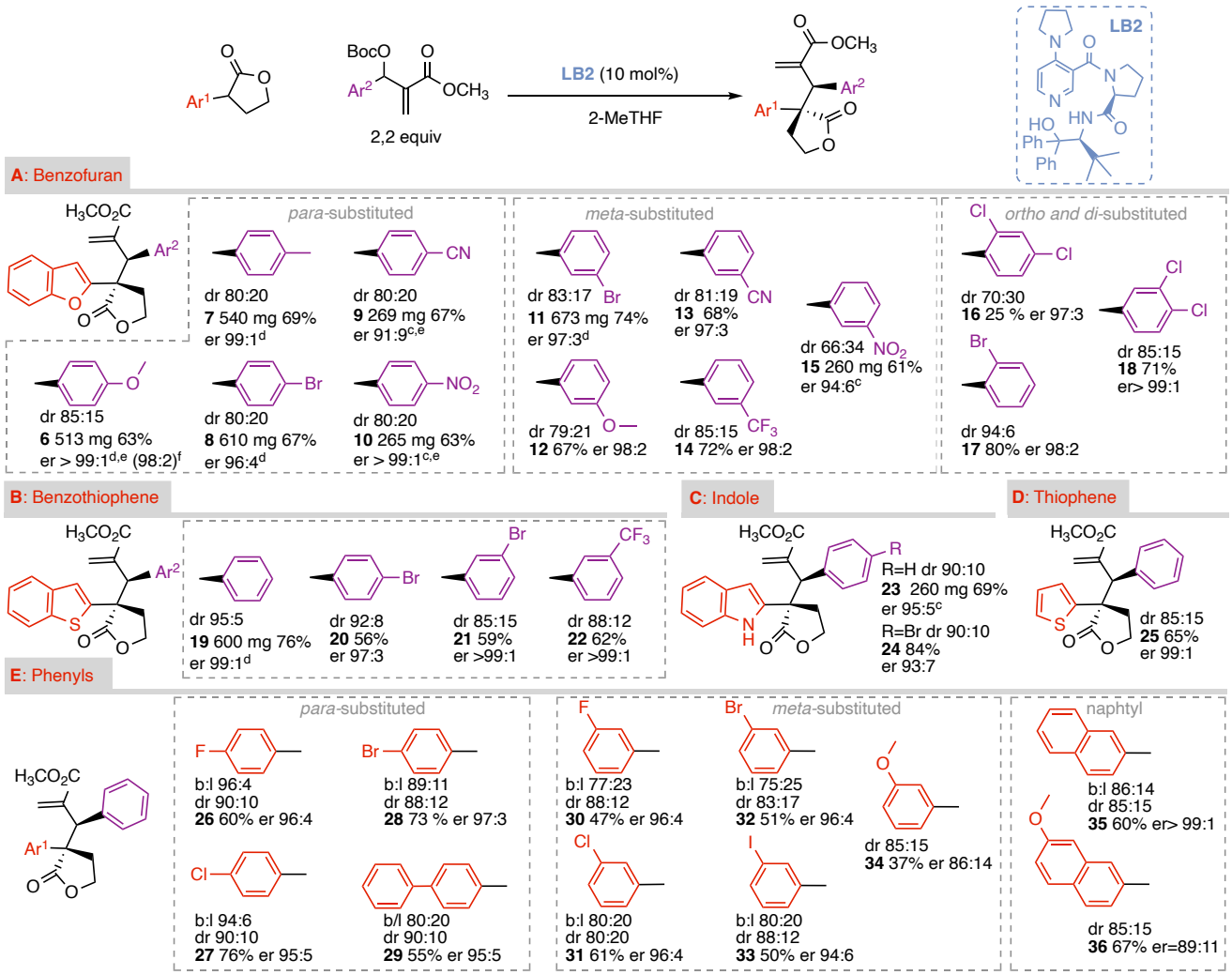
The benchmark study was carried out using lactone **1** as a model substrate for α-aryl-γ-butyrolactone and using 1.2 equivalent of MBH carbonate **2** (Scheme 2). Preliminary investigations using DMAP as a Lewis base highlighted that the solvent has a pronounced influence on the regioselectivity of the reaction. Indeed, when the reaction was conducted in DMF racemic linear product **3** was mainly formed (branched/linear ratio of 5/95) and isolated (Scheme 2, A). Interestingly, a reverse regioselectivity was observed when nonpolar solvents were involved culminating with the absence of the linear product in the crude reaction mixture when toluene was used. Good diastereoisomeric ratio (dr 14:86) for the desired branched product was observed and the major diastereoisomer **4** was isolated in high yield (79%) (Scheme 2, B). The relative configuration of created stereocenters in compound **4** was unambiguously determined by single crystal X-ray analysis. We further observed that a high regioselectivity in favor of the desired branched product (b:l 95:5) was maintained in toluene when 5 mol% of **LB1** was used as catalyst (Scheme 2, C). Noteworthy, in these reaction conditions, a good level of diastereoselectivity is maintained but with an opposite trend. The major diastereoisomer **5** was isolated in 40% yield and with an excellent 98:2 enantiomeric ratio. Further extensive exploration of various reaction conditions including solvents, stoichiometry of reactants and catalysts as well as catalyst structure was performed (see the ESI for details). Eventually, optimized reaction conditions involving the use of 10 mol% of **LB2** as catalyst and 2-methyltetrahydrofuran as solvent highlighted a virtual total regioselectivity (b:l>97:3) and a good diastereoselectivity (dr 84:16) (Scheme 2, D). Thus lactone **5** was isolated in a good yield (79%) and an excellent enantiomeric ratio (er 98:2).

Scheme 2. Regioselectivity, diastereoselectivity and enantioselectivity of organocatalyzed AAA with α-aryl-γ-butyrolactone **1**



With these optimized conditions in hand, we next explored the scope of the reaction (Scheme 3). MBH carbonates possessing diverse electronic properties were examined using lactone **1** as nucleophile partner in optimized reaction conditions (scheme 3, A). In all cases total conversion is reached in less than 8 h and a virtually total regioselectivity is observed (b:l>97:3). The MBH-carbonate bearing phenyl ring substituted either by electron donating or electron withdrawing groups gave good diastereoisomeric ratios (dr 80:20 to 94:6). The major diastereoisomer was isolated in all cases and robustness of the methodology was consolidated by experiments on 1 or 2 mmol scales. Starting from electron MBH-carbonates bearing 4-CH_3O and 4-CH_3-phenyl substitution, lactones **6** and **7** were obtained in good yields (63% and 69%) and excellent enantiomeric ratios (98:2 and 99:1). Notably use of deficient phenyl ring MBH-derivatives didn't compromise enantioselectivities of the AAA. Indeed lactones **8-10** were obtained in good yields (63-67%) and in high enantiomeric ratios (er 96:4 to 99:1). MBH carbonates embedding various meta substituents on the aryl group can be efficiently engaged in diastereoselective AAA (dr 66:33 to 85:15) and the major diastereoisomers (**11** to **15**) were isolated in good yields (up to 74 %) and good enantiomeric ratios (from 94:6 to 98:2). The absolute configuration of the created stereocenters were unambiguously determined by single crystal X-ray analysis of compounds **8** and **11**. Finally, chiral lactones **16-18** bearing ortho and disubstituted phenyl can be obtained in high enantiomeric ratios (up to >99:1) through a moderate to highly diastereoselective AAA (dr up to 94:6). We next explored the reactivity of α-aryl-γ-butyrolactones bearing other heteroaromatic ring. To our delight lactone bearing α-benzothienyl ring is a highly competent substrate for AAA which proceeded in high regioselectivity (no trace of linear product) and high diastereoselectivity (dr 95:5) (scheme 3, B). In this way lactone **19** was obtained in good yield and excellent enantiomeric ratio (99:1) on a 2 mmol scale experiment. The absolute configuration of lactone **19** was attributed by X-ray analysis.

Scheme 3. Scope of organocatalyzed AAA of α-aryl-γ-butyrolactone[a,b]

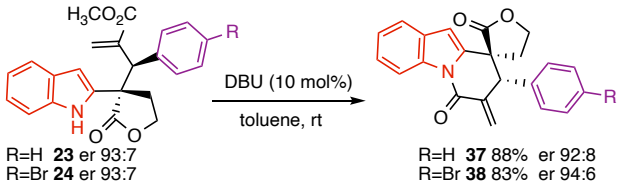


[a]Unless specified, the reactions were carried out with 0.25 mmol of lactone, 0.55 mmol of MBH-carbonate and 0.025 mmol of catalyst **LB2** in 2-MeTHF (2 mL). [b]b:l and dr were determined by ^{1}H NMR of the crude reaction mixture. The b:l ratio was >97:3 (linear product not detected in the ^{1}H NMR spectra) when not mentioned. er was determined by chiral HPLC analysis. Absolute configuration was assigned by single crystal X-ray analysis for compounds **8**, **11**, **19**, **27** and **28** and attributed by analogy for others. [c]Reaction carried out on 1 mmol scale. [d]Reaction carried out on 2 mmol scale. [e]yield and er after recrystallization. [f]er before recrystallization.

Gratefully, the AAA of α-benzothienyl-γ-butyrolactones with other MBH derivatives proceeded in equally high regioselectivities and stereoselectivities as demonstrated by the procurement of enantioenriched lactones **20**-**22** (er up to >99:1). Lactones embedding unprotected indole rings are a particularly interesting class of compounds for further applications of the methodology to the synthesis of biologically active compounds. The AAA also proceeded in virtually total regioselectivity and high diastereoselectivity affording the corresponding lactones **23** and **24** in high yields (69% and 84%) and enantioselectivities (95:5 and 93:7) (scheme 3, C). Good diastereoselectivities were also observed when α-thienyl-γ-butyrolactones were used and lactone **25** was obtained in an excellent enantioselectivity (er 99:1) (Scheme 3, D). The simple α-phenyl-γ-butyrolactones as well as the one embedding an electron rich substituent at the para position and ortho-substituted-α-phenyl-γ-lactones highlighted a poor reactivity in this process and no significant amount of the desired branched product can be isolated. However, substrates containing halogen atom at the para position afforded the corresponding branched major diastereoisomers (**26**-**29**) in moderate to good yields (55% to 76%) and high enantiomeric ratios (95:5 to 97:3) (Scheme 3, E). Nevertheless, and contrary to the class of substrates previously described, the presence of linear product was observed in some cases. The single X-ray analysis of compounds **27** and **28** confirmed that the stereoinduction of the AAA is identical to the one previously observed for the lactones substituted by heteroaromatic rings. The lactones bearing a meta substituted phenyl ring were less favorable substrates as a significant amount of a linear product (b:l up to 75:25) was observed in the crude reaction mixture. However, the reaction proceeded in good diastereoselectivities. The major diastereoisomers **30**-**34** were thus isolated in moderate yields (37 % to 61 %) and good enantiomeric ratios (86:14 to 96:4). The current process also occurred with the α-naphthyl lactone group, providing enantioenriched **35** and **36**

in moderate and excellent enantiomeric ratios (89:11 and 99:1). An important aspect of the present methodology is that it allows the construction of a quaternary stereocenter in the benzylic position of heteroaromatic compounds and the functionality introduced by the AAA process can thus be further exploited to access quickly to polycyclic chiral compounds. To illustrate this, indoyl lactones **23** and **24** were converted in polycyclic chiral compounds using a catalytic amount of DBU in toluene at room temperature (Scheme 4). The corresponding lactones **37** and **38** were isolated in good yields (88 and 83 %), and as expected, this transformation occurred with no depletion of enantioenrichment.

Scheme 4. Synthetic useful transformation: access to polycyclic indoyl compounds



In summary, we have developed an organocatalyzed AAA which allowed the direct functionalization of α-phenyl-γ-butyrolactones. This work demonstrates that this reaction proceeds in high regio-, diastereo-, and enantioselectivities affording chiral compounds with adjacent quaternary and tertiary stereocenters. Contrasting with previously described methodologies, a wide range of diastereoisomerically pure and highly enantioenriched lactones bearing heteroaromatic rings have been isolated in good yields. The expected mechanism of this AAA most probably occurs through an SN2′/SN2′ mechanism. However, the stereoelectronic features of the expected allyl-pyridinium intermediate and its interaction with the lactone enolate in the transition state entailing a high stereoselectivity could not be easily established and are under investigation in our group. The high functionality obtained can be exploited notably for the synthesis of chiral polycyclic compounds. Noteworthy, the created structures embed a 1,5-hexadiene scaffold where one $\boldsymbol{\pi}$ bond is part of an aromatic ring, which provides the opportunity to investigate the elusive aromatic Cope reaction.[4, 10] Investigation on this understudied reactivity is ongoing in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, copies of NMR spectra and HPLC chromatograms of all new compounds and X-ray crystallographic structures of (±)-**4** CCDC 2176403, **8** CCDC 2176404, **11** CCDC 2176405, **19** CCDC 2176406, **27** CCDC 2176407, **28** CCDC 2176408. (PDF)

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Author Contributions

E.R. proposed the project and performed preliminary study. E.R. and F.G. supervised the project and outlined a general strategy. M.M. conducted the experimental study, refined the approach, collected, and analyzed the data. M.F. performed the preliminary experiments on regioselectivity and diastereoselectivity. C.K collected and refined the X-ray diffraction data. E.R. and F.G. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

1.(a) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M., Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules. *Acc. Chem. Res.* **2015**, *48*, 740-751.(b) Quasdorf, K. W.; Overman, L. E., Catalytic enantioselective synthesis of quaternary carbon stereocentres. *Nature* **2014**, *516*, 181-191.(c) Trost, B. M.; Jiang, C., Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters. *Synthesis* **2006**, 369-396.

2.(a) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist Jr, J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M., Enantioselective Decarboxylative Alkylation Reactions: Catalyst Development, Substrate Scope, and Mechanistic Studies. *Chem. Eur. J.* **2011**, *17*, 14199-14223.(b) Hong, A. Y.; Stoltz, B. M., The Construction of All-Carbon Quaternary Stereocenters by Use of Pd-Catalyzed Asymmetric Allylic Alkylation Reactions in Total Synthesis. *Eur. J. Org. Chem.* **2013**, 2745-2759.(c) James, J.; Jackson, M.; Guiry, P. J., Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation: Development, Mechanistic Understanding and Recent Advances. *Adv. Synth. Catal.* **2019**, *361*, 3016-3049.

3.(a) James, J.; Guiry, P. J., Highly Enantioselective Construction of Sterically Hindered α-Allyl-α-Aryl Lactones via Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation. *ACS Catal.* **2017**, *7*, 1397-1402.(b) Nascimento de Oliveira, M.; Fournier, J.; Arseniyadis, S.; Cossy, J., A Palladium-Catalyzed Asymmetric Allylic Alkylation Approach to α-Quaternary γ-Butyrolactones. *Org. Lett.* **2017**, *19*, 14-17.

4.Bos, M.; Riguet, E., Iridium-catalysed asymmetric allylic alkylation of benzofuran γ-lactones followed by heteroaromatic Cope rearrangement: study of an unusual reaction sequence. *Chem. Commun.* **2017**, *53*, 4997-5000.

5.Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L., Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855-1969.

6.(a) Liu, T.-Y.; Xie, M.; Chen, Y.-C., Organocatalytic asymmetric transformations of modified Morita-Baylis-Hillman adducts. *Chem. Soc. Rev.* **2012**, *41*, 4101-4112.(b) Rios, R., Organocatalytic enantioselective methodologies using Morita-Baylis-Hillman carbonates and acetates. *Catal. Sci. Technol.* **2012**, *2*, 267-278.

7.(a) Alvin Tan, C. X.; Mei, G.-J.; Lu, Y., Phosphine-Catalyzed Asymmetric Allylic Alkylation of Achiral MBH Carbonates with 3,3′-Bisindolines: Enantioselective Construction of Quaternary Stereogenic Centers. *Org. Lett.* **2021**, *23*, 1787-1792.(b) Zhang, J.; Wu, H.-H.; Zhang, J., Enantioselective Phosphine-Catalyzed Allylic Alkylations of mix-Indene with MBH Carbonates. *Org. Lett.* **2017**, *19*, 6080-6083.

8.(a) Kamlar, M.; Hybelbauerova, S.; Cisarova, I.; Vesely, J., Organocatalytic enantioselective allylic alkylation of MBH carbonates with β-keto esters. *Org. Biomol. Chem.* **2014**, *12*, 5071-5076.(b) Liu, C.; Tan, B.-X.; Jin, J.-L.; Zhang, Y.-Y.; Dong, N.; Li, X.; Cheng, J.-P., Chiral biscinchona alkaloid promoted asymmetric allylic alkylation of 3-substituted benzofuran-2(3H)-ones with Morita-Baylis-Hillman carbonates. *J. Org. Chem.* **2011**, *76*, 5838-5845.(c) Jiang, K.; Peng, J.; Cui, H.-L.; Chen, Y.-C., Organocatalytic asymmetric allylic alkylation of oxindoles with Morita-Baylis-Hillman carbonates. *Chem. Commun.* **2009**, 3955-3957.(d) van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H., Construction of Adjacent Quaternary and Tertiary Stereocenters via an Organocatalytic Allylic Alkylation of Morita–Baylis–Hillman Carbonates. *Adv. Synth. Catal.* **2007**, *349*, 281-286.

9.Mando, M.; Grellepois, F.; Riguet, E., Organocatalytic enantioselective allylic alkylation of α-aryl γ-lactones: an approach to densely functionalized quaternary stereocentres. *Chem. Commun.* **2020**, *56*, 6640-6643.

10.Tomiczek, B. M.; Grenning, A. J., Aromatic Cope rearrangements. *Org. Biomol. Chem.* **2021**, *19*, 2385-2398.