CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201803677

Link to VoR: http://dx.doi.org/10.1002/chem.201803677

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10.1002/chem.201803677

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Decarboxylative Organocatalytic Allylic Amination of Morita-Baylis-Hillman Carbamates

Vojtěch Dočekal,[a] Michal Šimek,[a] Martin Dračínský[b] and Jan Veselý*[a]

Dedicated to Prof. Martin Kotora to his 55th anniversary.

Abstract: *The present study reports the organocatalytic enantioselective allylic amination of Morita-Baylis-Hillman carbamates efficiently catalyzed with chiral amine in the presence of Brønsted acid. Chiral allylic amines were produced in high yields (up to 98%) and enantioselectivities (up to 97% ee). This method provides an efficient and easily-performed route to prepare α-methylene-β-lactams, and other optically active β-lactams, such as the cholesterol-lowering drug Ezetimibe.*

Optically active allylic amines have been recognized as valuable building blocks with wide applications in the synthesis of biologically active and naturally occurring molecules.[1] Consequently, the development of efficient enantioselective synthetic methods for their preparation has generated considerable research interest.[2] Among the various methods used for this purpose,[3] direct amination via *aza*-Morita-Baylis-Hillman (*aza*-MBH) reaction[4] and transition metal and organocatalyzed asymmetric allylic amination (AAA)[5] stand out as some of the most powerful approaches.

Aza-MBH reaction is a highly efficient and atom-economic carbon-carbon forming reaction. Unfortunately, direct *aza*-MBH reaction is limited when applied to electron-rich imines, such as *N*-aromatic imines.[4] AAA methods predominantly use either transition metal complexes[6],[7] or chiral amines[8] and phosphines[9] as efficient catalysts, when racemic MBH derivatives, such as carbonates and acetates, serve as substrates. In comparison to direct *aza*-MBH reaction, AAA of conventionally used MBH derivatives is a less atom-economic approach because this process requires introducing a function group and subsequent removing it during the allylation step (Figure 1).

Despite the impressive advances made in *aza*-MBH and AAA methods, the development of atom-economic catalytic enantioselective amination reactions is still highly desirable. Considering the above and our interest in enantioselective allylic amination reaction,[8o,10] we report the enantioselective AAA of MBH carbamates and its application to the synthesis of biologically relevant motifs.

Because carbamates and carbamic acids can easily undergo decarboxylation to generate the corresponding amines,[11] we began testing the reactivity of racemic aniline-derived carbamates **1** in decarboxylative allylic amination using conventional nitrogen and phosphine nucleophiles as catalysts (Table 1). Fortunately, the model reaction of **1a** performed in toluene at room temperature was efficiently catalyzed with DABCO, generating allylic amine **2a** in an almost quantitative yield. Next, we enantioselectively validated our working hypothesis. Conventionally used *β*-isocupreidine efficiently catalyzed the model reaction, albeit with low enantiocontrol (entry 2). Other *β*-isocupreidine derivatives failed to show a higher enantiocontrol of decarboxylative AAA (see Table S1 in SI file). Significantly reduced reactivity was observed under catalysis with quinine and cinchonidine (entries 3, 4), with no full conversion of **1a**, even after lengthening the reaction time to 7 days. Conversely, significantly enantiomerically enriched **2a** was generated in the presence of dimeric *Cinchona*-based tertiary amines, such as $(DHQD)_2AQN$ and $(DHQ)_2AQN$, albeit in low yields (entries 5, 6). Other screened catalysts, including Kwon's catalyst (entry 7), other Sharpless bases and phosphine-(thio)urea catalysts previously developed in our group failed to efficiently catalyze the model reaction (see Table S1 in SI file).

Based on the above, we chose $(DHQD)_2AQN$ as an appropriate catalyst for subsequent optimization of reaction conditions. According to our observations (Table 1), this reaction tolerates a wide range of non-polar solvents, such as aromatic, etheral and chlorinated solvents, in addition to a polar protic solvent. Performing the model reaction in chlorinated solvents and ethers led to the formation of product **2a** in moderate yields and enantioselectivities (entries 11-14), whereas higher yields and enantioselectivities of **2a** were achieved in aromatics (entries 8-10). Based on the screening results (see also Table S2 in SI file), bromobenzene was selected as the most suitable solvent because **2a** was obtained in high yield (75%) and enantioselectivity (82% *ee*, entry 9).

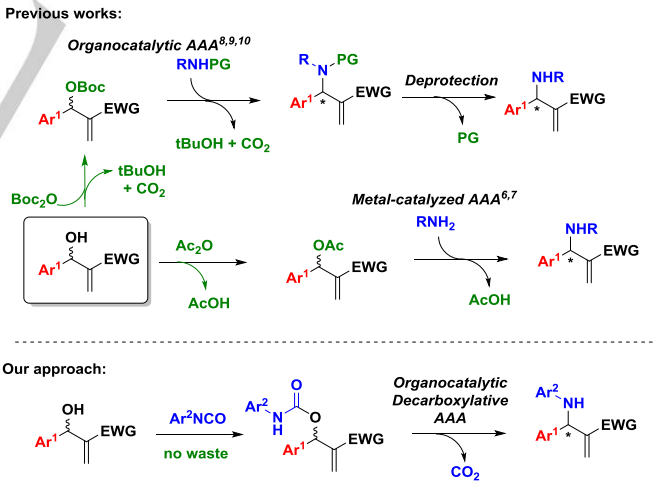

Figure 1. Previous approaches towards preparation of MBH-derived chiral amines.

[a] V. Dočekal, M. Šimek, Dr. J. Veselý
Department of Organic Chemistry
Charles University
Hlavova 8, 12843 Prague, Czech Republic
E-mail: jxvesely@natur.cuni.cz, http://orgchem.cz/vesely/
[b] Dr. M Dračínský
Institute of Organic Chemistry and Biochemistry
Czech Academy of Sciences
Flemingovo nám. 2, 16610 Prague, Czech Republic

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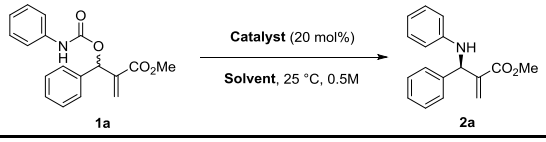
Table 1. Screening of chiral tertiary amine catalysts and optimization studies



Entry	Catalyst	Solvent	Time [h]	Yield [%][a]	*e.e.* [%][b]
1	DABCO	toluene	16	90	-
2	*β*-ICD	toluene	16	76	29
3[c]	quinine	toluene	168	20	-16
4[c]	cinchonidine	toluene	168	30	19
5[c]	$(DHQD)_2AQN$	toluene	168	62	82
6[c]	$(DHQ)_2AQN$	toluene	168	44	-64
7[d]	Kwon cat.	toluene	168	n.d.	n.d.
8[c]	$(DHQD)_2AQN$	benzene	168	66	80
9	$(DHQD)_2AQN$	bromobenzene	112	75	82
10[c]	$(DHQD)_2AQN$	mesitylene	168	50	84
11	$(DHQD)_2AQN$	DCM	112	75	65
12[c]	$(DHQD)_2AQN$	$CHCl_3$	168	42	63
13[c]	$(DHQD)_2AQN$	Et_2O	168	45	73
14[c]	$(DHQD)_2AQN$	MTBE	168	39	75
15	$(DHQD)_2AQN$	MeOH	60	59	60

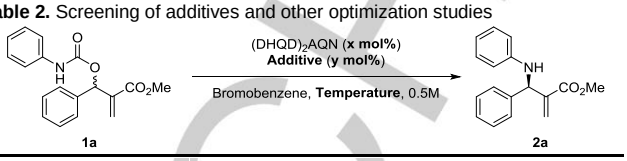
[a] Isolated yield after column chromatography. [b] Determined by HPLC of purified product **2a**. [c] No full conversion of **1a** was observed. [d] No reaction.

Subsequently, the presence of an additional Brønsted acid showed a strong effect on reactivity and on asymmetric induction (Table 2). When optically active camphorsulfonic acid - (1*S*)-CSA, was used together with $(DHQD)_2AQN$, allylic amine **2a** was obtained in high enantiomeric purity (94% *ee*, entry 4).[12] Conversely, the co-catalytic system $(DHQD)_2AQN$/(1*R*-CSA) failed to significantly increase asymmetric induction. This observation may be explained by the stereochemical "match-mismatch" effect of the two sources of chirality and catalysts. The results from the $(DHQ)_2AQN$/(1*S*)CSA (and 1*R*-CSA) cocatalytic system support the above effect on the enantiocontrol of the process (entries 12-13).

The reaction temperature and concentration had a marked effect on reaction efficiency and enantioselectivity. Enantiocontrol slightly decreases at high temperatures (entries 6-7), and an increased concentration of **1a** significantly shortened the reaction time (entries 8, 9). Thus, a model reaction of **1a** catalyzed with $(DHQD)_2AQN$/(1*S*)-CSA in bromobenzene (*c* = 2 mol/l) at 40°C generated allylic amine **2a** in an 87% yield and with high enantioselectivity (93% *ee*) in 44 h (entry 9).

Then, we analyzed the variation in reaction efficiency with catalyst loading and with the $(DHQD)_2AQN$/(1*S*)-CSA ratio. Interestingly, no change in enantioselectivity was observed with the increase in CSA, until an excess of CSA to $(DHQD)_2AQN$ was used. The 2:1 ratio of $(DHQD)_2AQN$/(1*S*)-CSA was found to be optimal for the model reaction (see SI file). No change in reaction efficiency was observed when using reduced quantities of catalysts, 10 mol % $(DHQD)_2AQN$ and 5% (1*S*)-CSA (entry 10). Further reduction of catalyst loading had a deleterious effect on the reaction yield (entry 11).

Table 2. Screening of additives and other optimization studies



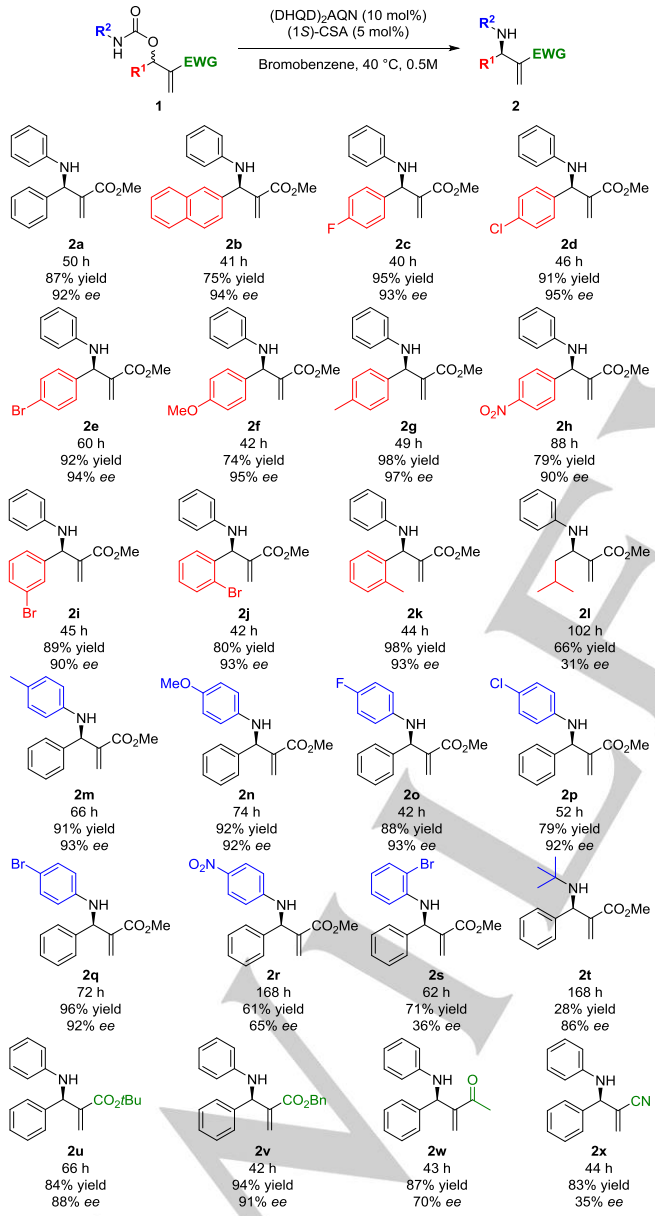
Entry	$(DHQD)_2AQN$ [x mol %]	Additive [y mol %]	Temp.	Time [h]	Yield [%][a]	*e.e.* [%][b]
1[c]	20	2,4-DNBA, [10]	25 °C	168	68	82
2[c]	20	*p*-TsOH, [10]	25 °C	168	56	85
3[c]	20	BNHP, [10]	25 °C	168	66	86
4[c]	20	(1*S*)-CSA, [10]	25 °C	168	68	94
5[c]	20	(1*R*)-CSA, [10]	25 °C	168	76	86
6	20	(1*S*)-CSA, [10]	40 °C	168	79	92
7	20	(1*S*)-CSA, [10]	80 °C	20	76	86
8[d]	20	(1*S*)-CSA, [10]	40 °C	68	88	93
9[e]	20	(1*S*)-CSA, [10]	40 °C	44	87	93
10[e]	10	(1*S*)-CSA, [5]	40 °C	50	87	92
11[c,e]	5	(1*S*)-CSA, [2.5]	40 °C	168	53	92
12[c,f]	20	(1*S*)-CSA, [10]	40 °C	168	42	-66
13[c,f]	20	(1*R*)-CSA, [10]	40 °C	168	68	-83

[a] Isolated yield after column chromatography. [b] Determined by HPLC of purified product **2a**. [c] No full conversion of **1a** was observed. [d] *c* = 1.0 mol/l. [e] *c* = 2.0 mol/l. [f] Reaction with $(DHQ)_2AQN$.
2,4-DNBA = 2,4-Dinitrobenzoic acid, BNHP = (*R*)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate, (1*S*)-CSA = (1*S*)-(+)-Camphorsulfonic acid, (1*R*)-CSA = (1*R*)-(+)-Camphorsulfonic acid, 2.4-DNBA = 2,4-Dinitrobenzoic acid.

After optimizing the reaction conditions, we began exploring the scope of organocatalytic decarboxylative AAA reaction by varying the MBH carbamate **1** (Scheme 1). The corresponding allylic amines **2c-g**, derived from MBH carbamates containing both electron withdrawing (EWG) and donating (EDG) groups in the *para* position of the aromatic ring, were produced in high yields (74-98%) with excellent enantioselectivities (90-97% *ee*). When a strong EWG such as substrate **1h** was present, the reaction rate decreased slightly; otherwise, the reaction was completed within 2 days. Moreover, *ortho*- and *meta*-substituted MBH carbamates **2i-k** showed similar levels of reactivity and enantiocontrol under the reported reaction conditions. For example, the MBH carbamate **1k** reaction generated chiral allylic amine **2k** (with the *o*-methyl group) in a nearly quantitative yield (98%) and with 93% *ee*.

10.1002/chem.201803677

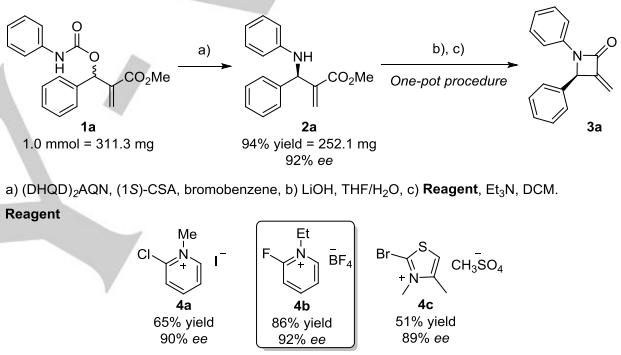
Then, we examined MBH carbamates derived from various anilines under optimized reaction conditions (Scheme 1). The results showed that *para*-substituted aniline-derived MBH carbamates had a significant electronic effect on reaction rate and on selectivity. When electron rich aniline-derived carbamates **1m** or **1n** were subjected to the reaction, the corresponding products were generated in excellent yields and with high levels of enantioselectivity. MBH carbamates with electron-demanding substituents also produced amines **2o-q** in high yields and enantioselectivities, except strongly electron demanding aniline-derived substrates. For example, substrate **1o** led to formation of **2o** in 88% yield and with 93% *ee*, whereas compound **2r** was produced in low yield and with moderate enantioselectivity (65% *ee*) after a prolonged reaction time.



Scheme 1. Substrate scope of decarboxylative AAA using MBH-carbamates.

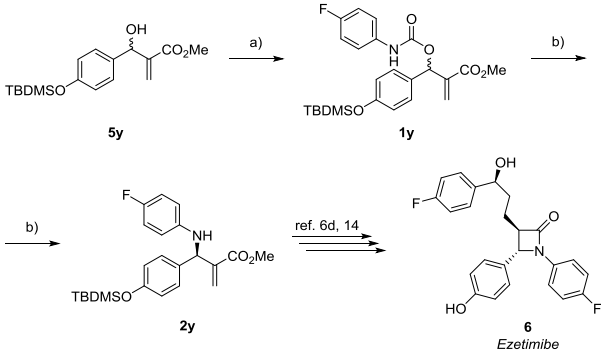
Significantly reduced enantiocontrol was also observed when *ortho*-substituted aniline-derived MBH carbamate **1s** was used. This may be explained by the electron-deficient behavior of the aniline part and by steric hindrance. Interestingly, sterically demanding aliphatic amine-derived substrate **1t** generated the corresponding product in low yield but with 86% *ee*. This clearly shows that electronic effects primarily account for reduced enantiocontrol. We also examined other MBH carbamates, such as carbamates derived from other aliphatic amines, aliphatic MBH alcohols, and MBH carbamates derived from various electron deficient alkenes, but most corresponding products, **2l** and **2u-x**, showed reduced enantioselectivity (Scheme 1).

To evaluate this organocatalytic asymmetric system on a large scale, 1.0 mmol of allylic carbamate **1a** was used to perform the AAA reaction, and the product **2a** was obtained in 94% yield and with 92% *ee* (Scheme 2). Furthermore, the allylic amine **2a** was converted into *α*-methylidene-*β*-lactam **3a** using pyridinium salts **4**. When tetrafluoroborate **4b** was used, the lactam **3a** was obtained in excellent yield (86%) with retained enantioselectivity (92% ee).



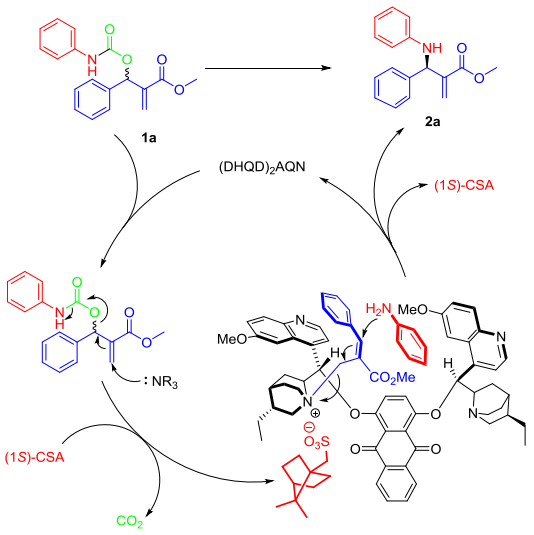
Scheme 2. Synthesis of enantiomerically enriched *α*-alkylidene-*β*-lactam **3a**.

Enantiomerically enriched allylic amines **2** and *α*-methylidene-*β*-lactams **3** are useful synthetic intermediates. For example, allylic amine **2y**, prepared by enantioselective decarboxylative AAA of **1y**, can be readily transformed into Ezetimibe,[13] a strong cholesterol absorption inhibitor (Scheme 3).[6d,14]



Scheme 3. Formal total synthesis of Ezetimibe.

The absolute configuration of allylic amines **2** and the corresponding *α*-methylidene-*β*-lactam **3** was assigned by single X-ray diffraction analysis[15] of compound **2e** (see SI file) and by chemical correlation.[16] The stereogenic center (C4) has (*R*)-absolute configuration. This observation is also supported by the proposed reaction mechanism (Scheme 4).



Scheme 4. Proposed reaction mechanism of the AAA reaction.

We hypothesize that the reaction mechanism proceeds via two key steps. First, a nucleophilic addition of the tertiary amine of the catalyst on the terminal carbon of the electronically poor double bond in compound **1a** leads to the formation of a positively charged intermediate while an aromatic carbamate anion is expelled. The carbamate anion may undergo protonation, by the camphorsulfonic acid, and decarboxylation, thereby leading to an aniline derivative. The second step of the reaction involves a nucleophilic addition of the aniline on the intermediate leading to the final product **2a** and to the release of the catalyst. The camphorsulfonate anion may facilitate the loss of the excess proton in the final product.

To support the proposed mechanism, we performed a computational search for possible transition-state (TS) structures at the DFT level. Because the $(DHQD)_2AQN$ catalyst is a rather large molecule, we performed the TS search with a smaller model consisting of 5-methylquinuclidin-2-yl-ethan-1-ol, as shown in Figure 2. We found transition states structures with modest energy barriers of 147 and 93 kJ/mol, respectively, for both proposed key steps of the AAA reaction. The structure of the intermediate with the covalently linked catalyst is crucial for the stereochemical outcome of the reaction. Therefore, we also performed a DFT search for the conformation with the lowest energy intermediate without any truncation of the catalyst structure, and we found that the *Si* face of the double bond is blocked by the quinuclidine and by the quinolone part of the catalyst in this conformation, thus leaving the *Re* face exposed to the addition of the aniline. This preferred conformation supports the formation of the final product with *R* configuration, in agreement with the experimental findings.

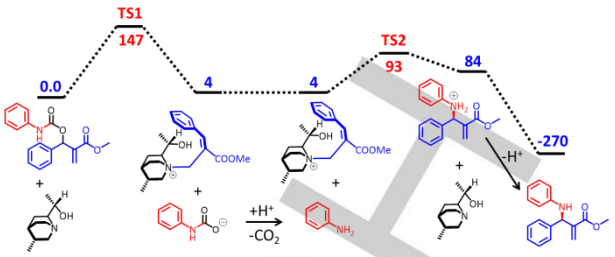


Figure 2. Calculated (B3LYP/6-31g(d,p)) relative energy profile of the AAA reaction. All energies are expressed as kJ/mol.

In summary, we developed and optimized a method for the organocatalytic decarboxylative enantioselective allylic amination of readily available Morita-Baylis-Hillman carbamates. The reaction is efficiently catalyzed by combining the co-catalytic systems $(DHQD)_2AQN$ and (1*S*)-CSA, generating chiral allylic amines in excellent yields and enantioselectivities. We showed that this method can be used for the preparation of *α*-methylene-*β*-lactams in a simple lactamization reaction. Moreover, the synthetic utility of the protocol is exemplified by the formal synthesis of a blockbuster drug, Ezetimibe. The proposed reaction mechanism is still under investigation and ongoing mechanistic studies in our laboratory will provide further insights into this process.

Experimental Section

In a vial equipped with magnetic stirring bar, were placed $(DHQD)_2AQN$ (0.02 mmol, 0.1 eq.), (1*S*)-CSA (0.01 mmol, 0.05 eq.), MBH adduct **1** (0.2 mmol, 1.0 eq.) and bromobenzene (0.1 ml). Reaction mixture was stirred for indicated time at 40 °C. Solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane/EtOAc as an eluent.

Acknowledgements

JV thanks the Czech Science Foundation (No 16-23597S) for funding this study. VD thanks the Charles University Grant Agency (No 1504217) for the financial support and MD thanks the Czech Science Foundation (No 18-11851S). The authors also thank Dr. Hybelbauerová and Dr. Tošner for the NMR service, Dr. Štícha for the MS analysis, Dr. Císařová for the X-ray analysis, Dr. Kaminský for computational studies and Dr. Carlos V. Melo for proofreading.

Keywords: Enantioselective allylic aminination • Cinchona alkaloids • MBH derivatives • Brønsted acid • Chiral allylic amines

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10.1002/chem.201803677

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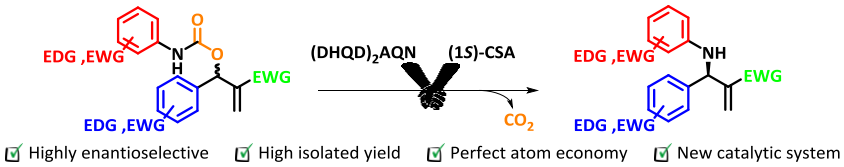

*Vojtěch Dočekal, Michal Šimek, Martin Dračínský, Jakub Kaminský, Jan Veselý**

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Decarboxylative Organocatalytic Allylic Amination of Morita-Baylis-Hillman Carbamates

Decarboxylative amination: Organocatalytic enantioselective allylic amination of Morita-Baylis-Hillman carbamates efficiently catalyzed with chiral amine in the presence of Brønsted acid produces chiral allylic amines in high yields (up to 98%) and enantioselectivities (up to 97% *ee*). This method provides an efficient, atom-economic and easily-performed route to prepare *α*-methylene-*β*-lactams and other optically active *β*-lactams.