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N-Heterocyclic Carbene-Catalyzed Enantioselective Intramolecular Annulations to Construct Benzo-Fused Pyranones with Quaternary Stereocenter

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Dedication to Professor Grzegorz Mlostoń on the Occasion of his 70th Birthday.

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Abstract. A highly enantioselective intramolecular NHC-catalyzed approach for the synthesis of benzo-fused pyranones bearing quaternary stereocenter is described. The developed methodology is based on annulation reaction between acyl anion intermediates and β,β-disubstituted Michael acceptors. The reaction offers streamlined and effective access to target products in a highly stereoselective manner.

Keywords: Organocatalysis, *Umpolung*, *N*-heterocyclic carbene, Stetter reaction

The stereocontrolled synthesis of specific structural motifs possessing at least one quaternary stereocenters is of the key challenges in the contemporary organic chemistry.[1–3] One of the difficulties in constructing quaternary carbons is their congested nature, wherein the creation of such centers is complicated by steric repulsion between the carbon substituents. Despite remarkable advances, such catalytic enantioselective creation of quaternary carbon stereocenters is still rather limited for this task.[4–6] Among biologically relevant molecules bearing such stereocenters, benzo-fused ketones such as chromanones and their tetralone derivatives appear in a variety of many bioactive natural products (with selected examples in **Figure 1** and have found interesting applications as building blocks and reagents in organic synthesis.[7–10]

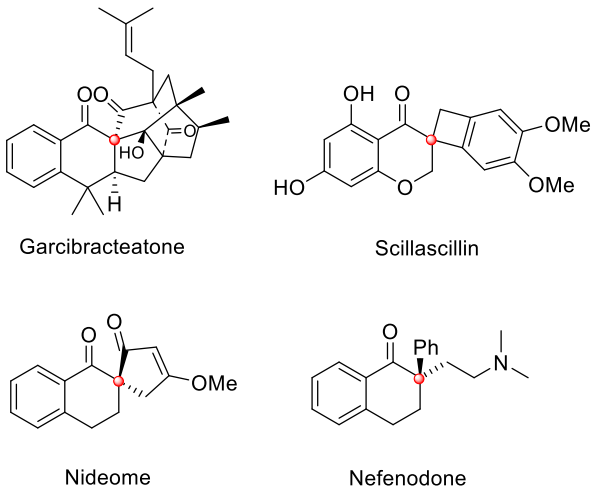
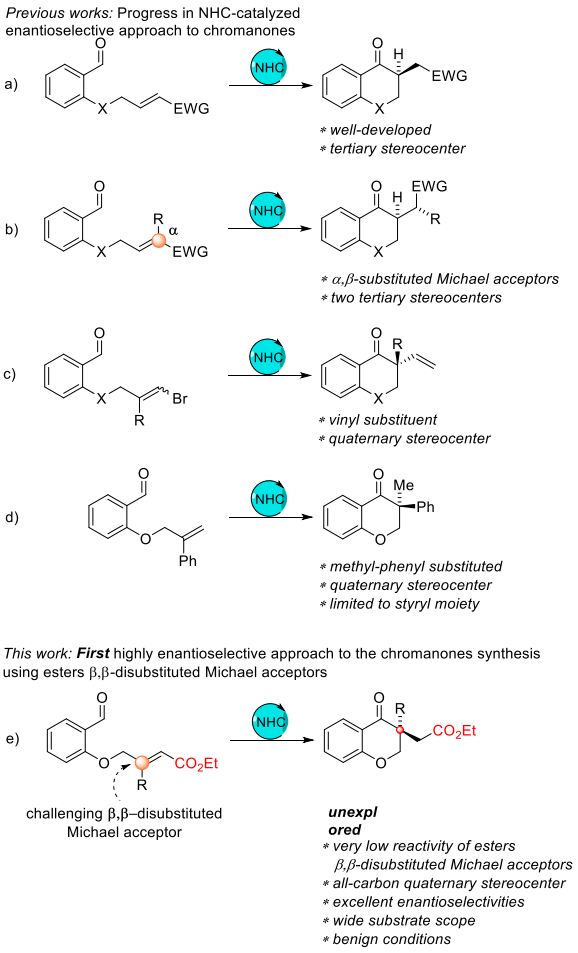


Figure 1. Natural products and bioactive molecules containing six-membered benzo-fused ketones.

For instance, garcibracteatone is a polycyclic polyprenylated acylphloroglucinol (PPAP) natural product, most structurally complex PPAP with a highly compact polycyclic ring system containing seven stereocenters, five of which are quaternary.[11] Additionally, homoisoflavonoids derived from scillascillin have been intensively investigated in the study for antiangiogenic activity.[12] The importance of benzo-fused cyclohexanones can be further exemplified by the natural occurring nideome which possess additionally spiro[4.5]decane carbon framework and also on other structurally important motif such as nafenodone as the antidepressant drug.[13,14] In recent years *N*-heterocyclic carbene catalysis has emerged as an attractive and ideal strategy to synthesize complex heterocyclic molecules *via* umpolung reactivity.[15–29] Among various asymmetric catalytic strategies for the stereoselective construction and selective functionalization of the six-membered motifs, the Stetter reaction proved to be one

of the universal and fundamental tool of the *N*-heterocyclic carbene (NHC) catalysis[30–36] After Ciganek initial contribution on intramolecular NHC-catalyzed synthesis of chromanones, during next years many highly enantioselective approaches have been developed (**Scheme 1**, eq a).[30,37–40] In the later stage, Rovis and coworkers disclosed a highly enantioselective and diastereoselective Stetter reaction of salicylaldehyde-derived bearing a tethered *α,β*-disubstituted Michael acceptors (eq b).[31] This transformation allowed to obtain chromanones with two tertiary stereogenic centers. More recently, Zhou group reported a selective approach to enantioenriched chromanones utilizing NHC-catalyzed intramolecular S_N2' nucleophilic substitution reaction (eq c).[41] Furthermore, Glorius demonstrated another way which offers access to chromanones bearing quaternary stereocenter though intramolecular hydroacylation of electron-neutral olefins (eq d).[42] However, it must be strongly emphasized, that this methodology is limited to the *O*-styryl moiety and as a result, only chromanones containing methyl-aryl substituents at the quaternary stereocenter are formed. The use of *β,β*-disubstituted Michael acceptors in the synthesis of five-membered rings containing fully substituted stereocenters is well known for a wide range of olefin activating groups.[43–45] Nevertheless, annulation to the six-membered rings *via* intramolecular Stetter reaction certain challenges related to the reactivity of these substrates had to be addressed. First, replacing the hydrogen atom in the *β*-position with an alkyl substituent generates additional spatial crowding, thereby reducing the acceptor's reactivity to a nucleophilic attack. Secondly, in contrast to synthesis of five-membered analogues, the heteroatom is directly bound in the *β*-position, thereby increasing the electrophilicity and reactivity of the double bond. It is not possible in the case of six-membered systems, *β,β*-disubstituted Michael acceptors, in particular ester derivatives, is not sufficiently activated under the conditions of the Stetter reaction. The absence of a heteroatom directly bond in the *β*-position results in a drastic reduction in reactivity. To the best of our knowledge, only one case of enantioselective approach to six-membered ring using ester *β,β*-disubstituted Michael acceptor is known in literature.[46]



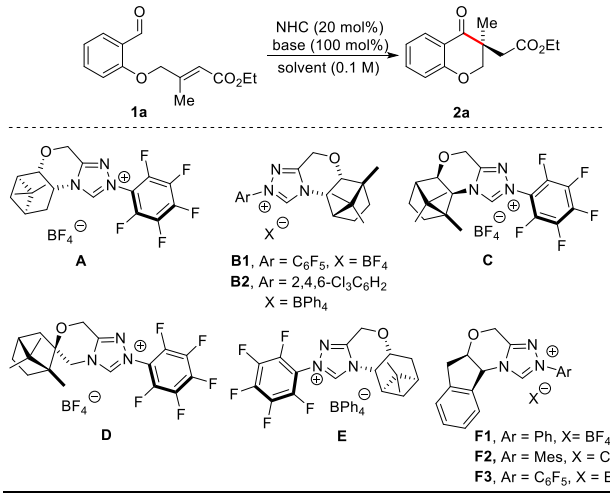
Scheme 1. NHC-Catalyzed intramolecular Stetter/substitution/hydroacylation reactions.

We envisioned that through the appropriate substrate construction, a proper choice of the NHC catalyst should enhance such a reactivity pattern ensuring a selectivity at the same time, thereby, enabling the reaction to proceed *via* a desired annulation (eq e). The catalytic, enantioselective formation of quaternary stereocenters has received a considerable amount of attention recently, yet remains a very challenging endeavor in organic synthesis. Herein, we report our studies on this novel approach for the synthesis of optically active chromanone derivatives bearing quaternary stereogenic center employing NHC chemistry. The developed strategy utilized *β,β*-disubstituted Michael acceptors as electron-deficient olefins.

The present studies were initiated by treating salicylaldehyde-derived *β*-methylacrylate **1a** with various optically pure *N*-substituted triazolium salts using different bases and solvents (**Table 1**). When pinene-derived triazolium salt **A** with an pentafluorophenyl group was chosen as a precatalyst with DIPEA in toluene, a pyranone skeleton with all-carbon quaternary stereocenter was constructed with great enantioselectivity (98% *ee*) and yield of 92%. Chiral catalyst **B1**, which bears a camphor skeleton as the stereo-inducing unit, gave also almost full conversion to the product with the same level of

enantioselectivity but as a opposite enantiomer. Replacing the *N*-C_6F_5 substituent of the NHC catalyst **B1** with 2,4,6-trichlorophenyl unit **B2** and tetraphenylborate anion as a counterion did not lead to the desired product. Similar effect was observed for the NHC-precatalyst **E** with the same tetraphenylborate counterion. Probably, the more sterically demanding BPh_4 counterion effectively prevents the attack of generated *in situ* acyl anion to the disubstituted Michael acceptor. Interestingly, catalyst **C** which possess switched amino and alcohol position and *endo,endo*-relation to the *gem*-dimethyl bridge exhibit quite high selectivity for the reaction albeit very low activity was observed (**Table 1**, entry 4). Most likely, the reason for such a low conversion is spatial congestion additionally enhanced by the methyl group located near the carbene center and decrease reactivity in the annulation process. Spirocyclic-derived NHC precatalyst **D** could also afford the desired benzannulated product with high yield but a reduced enantioselectivity of 40% *ee*. Aminoindanol-derived NHC precatalysts bearing *N*-Ph (**F1**) and *N*-Mes (**F2**) groups were not effective for this process, while the one bearing *N*-C_6F_5 (**F3**) group showed superior effectiveness provided the chromanone **2a** in an excellent yield and exceptional enantioselectivity 99.8% *ee*. Subsequent base screening (**Table 1**, entries 10-16) revealed, that different organic bases, even extremely strong ones such as BEMP or P_2-Et could give the products with high yields and without erosion of stereoselectivity, remaining at <99%. Additional screening of the reaction solvents did not show further improvements in the reaction outcomes (**Table 1**, entries 16-20). Finally, identification of diisopropylethylamine and toluene as the best-suited reaction conditions were indicated in terms of enantioselectivity for the developed annulation.

Table 1. Optimization of the Reaction Conditions.



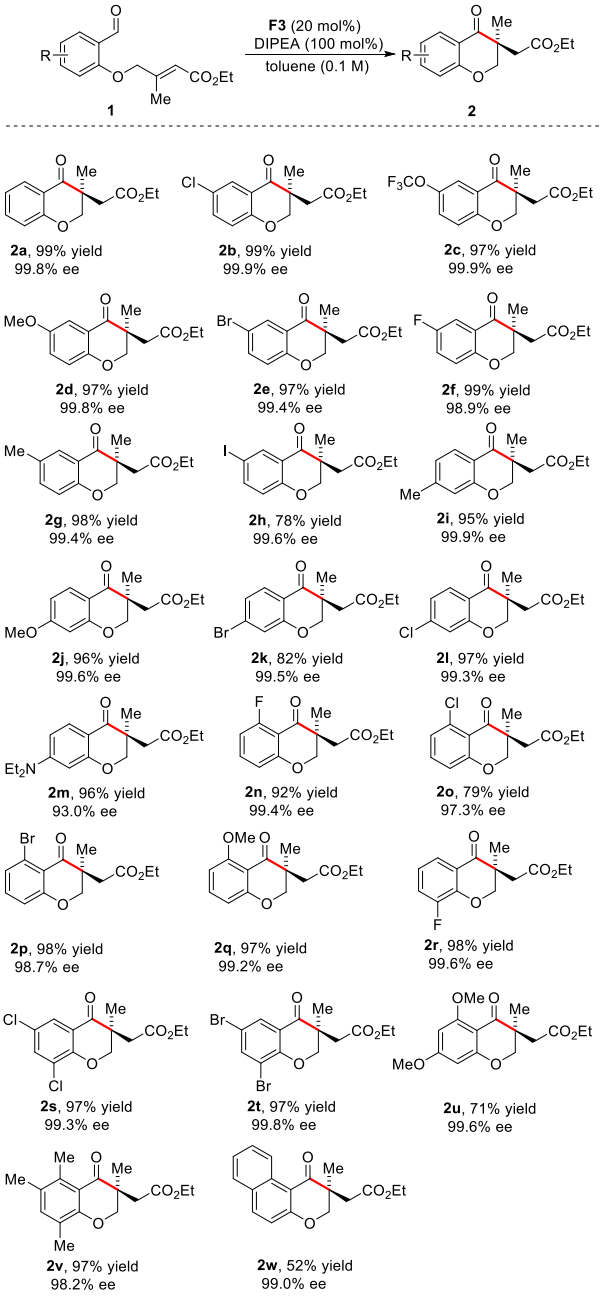
entry	preNHC	Base	Solvent	yield (%)[b]	*ee* (%)[c]
1	**A**	DIPEA	toluene	92	98
2	**B1**	DIPEA	toluene	94	98[d]
3	**B2**	DIPEA	toluene	---	---
4	**C**	DIPEA	toluene	10[e]	81
5	**D**	DIPEA	toluene	98	41
6	**E**	DIPEA	toluene	---	---
7	**F1**	DIPEA	toluene	---	---
8	**F2**	DIPEA	toluene	---	---
9	**F3**	DIPEA	toluene	99	99.8
10	**F3**	DCyEA	toluene	97	99.6
11	**F3**	BEMP	toluene	98	99.6
12	**F3**	Pempidine	toluene	96	99.6
13	**F3**	NMM	toluene	97	99.0
14	**F3**	DBU	toluene	85	98.2
15	**F3**	DABCO	toluene	88	98.0
16	**F3**	P_2-Et	toluene	89	99.1
17	**F3**	DIPEA	DCM	97	99.6
18	**F3**	DIPEA	THF	99	99.4
19	**F3**	DIPEA	Et_2O	97	99.4
20	**F3**	DIPEA	MTBE	95	99.5

[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale **1a** in solvent (2.0 mL) at room temperature. [b] Yields of isolated products. [c] *ee* values determined by HPLC on Phenomenex Lux Cellulose-1 column (see the SI). [d] Opposite enantiomer. [e] Reaction was performed for 48 h. Abbreviations: BEMP: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; Phosphazene base P_2-Et: 1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ5,4λ5-catenadi(phosphazene); DCyEA: Dicyclohexylethylamine.

Furthermore, the scope of this annulation using a wide range of substrates with different substitution patterns of the aromatic ring was examined. As shown in **Table 2**, a broad spectrum of salicylaldehyde-derived *β*-methylacrylates were explored and produced chromanone products in very high yield and

with excellent enantioselectivities. Initially the influence of the electron properties and position of substituents on the aromatic ring was investigated. The use of substrates with electron-withdrawing substituents at 5-position showed exceptional reactivity (**2b,c,e,f**). Surprisingly, 5-iodo derivative **2h**, was also tolerated affording the product with slightly lower yield, albeit without any loss of enantioselectivity. The use of 5-methoxy or 5-methyl groups as a electron-donating substituents leads to products **2d**,**g** in excellent yields and remarkably high enantioselectivities (99.4-99.8% *ee*). A similar trend was observed when the electron-donating methyl **2i** and methoxy **2j** groups were introduced in the 4-position of the aromatic ring giving the products almost quantitively with excellent optical purity (99.8-99.9% *ee*). The cyclization proceeded consistently for 4-substituted substrates carrying an electron-withdrawing groups on the aromatic ring (**2k**, **2l**). Notably, the reaction was found to tolerate diethylamino **2m** as a strong activation group having a tendency to increase of an undesired aldol-elimination side reaction, providing the product with 96% yield and with slightly decreased enantioselectivity (93% *ee*). Furthermore, we also examined the effect of substitution at 6-position on the reactivity and selectivity of the annulation process due to the close proximity of activating and deactivating groups in *ortho*-orientation. To our great delight, both electron-withdrawing (**2n-p**) and electron-donating (**2q**) substituents were well-tolerated to obtain the chromanones in good to excellent yields and level of enantioselectivity in all of the cases. In addition, 2-fluoro salicylaldehyde-derived was also investigated in the reaction, thereby affording the desired quaternary chromanone **2r** with comparable result. Next, we were pleased to find that the disubstituted and trisubstituted substrates with different substitution patterns of the aromatic ring undergoes the reaction smoothly and generate the corresponding chromanones (**2s-v**). Finally, naphtaldehyde-derived methylacrylate **1w** also readily cyclized to the target tricyclic naphthoannulated pyranone **2w** in high stereoselective fashion, however, with lower yield. The results show, the reaction proved unbiased towards the position of the substituents on the aromatic ring afforded the desired products with excellent stereocontrol. The absolute configuration of benzo-fused pyranones was assigned based on the assumption that the bias of the aminoindanol-NHC catalyst is identical for five-membered analogous, the absolute stereochemistry observed for six-membered skeletons would be consistent with those substrates reacting preffentially in *S*-configuration.[42],[46] Taking into account such high values of enantiomeric excesses generally obtained in the present study, it is reasonable to assume that all the benzannulated pyranones **2a**–**2zz** are formed with the same absolute configuration.

Table 2. Substrate Scope for the Synthesis of Chromanones with Quaternary Stereocenter[a].

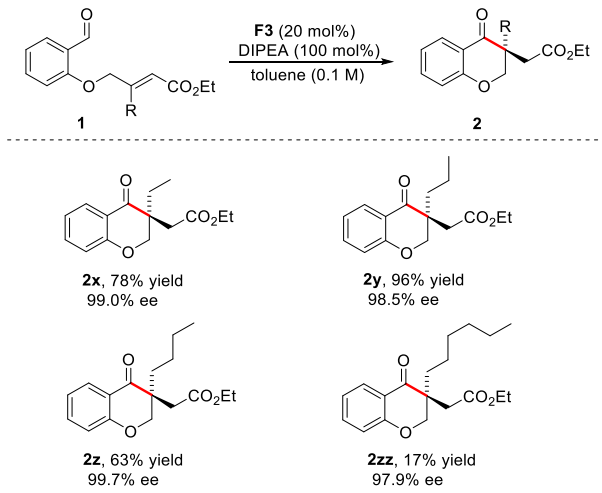


[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale in solvent (1.0 mL) at room temperature for 20 h. Yields of isolated products. *Ee* values determined by HPLC on Phenomenex Lux Cellulose-1 column (see the SI).

To further demonstrate the generality of this annulation, we also examined the use of various *β,β*-disubstituted Michael acceptors with different lengths alkyl chain substituent (**Table 3**). Delightfully, the extension of alkyl chain was well-tolerated without a significant influence on the outcome in terms of stereochemical efficiency. Nevertheless, as a results an increase in the alkyl chain length from the butyl substituent a significant decrease in chemical yield as demonstrated in the synthesis of **2z** (63%, 99.7% *ee*) and **2zz** (17%, 97.9% *ee*). Furthermore, we also decided to investigate sterically more hindered substituent in the *β*-position of the Michael acceptor

introduce the phenyl group instead of methyl substituent. However, using different reaction conditions (elevated temperature, microwaves) failed to obtain the desired product and only the starting material was recovered.

Table 3. Scope of β-alkyl-β-substituted Michael acceptors[a].



[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale in solvent (1.0 mL) at room temperature for 20 h. Yields of isolated products. *Ee* values determined by HPLC on Phenomenex Lux Cellulose-1 column (see the SI).

In summary, we have developed a highly asymmetric and new NHC-catalyzed annulation with the use of ester *β,β*-disubstituted Michael acceptors for efficient synthesis of chromanone derivatives bearing quaternary stereogenic center. A broad scope of substates worked well in this transformation affording the products with high yields and with exceptional enantioselectivities through simple operation. Application of long chain alkyl substituents in Michael acceptors is also possible giving the products without any loss of enantiocontrol. The robustness screen showed a very high tolerance of this reaction to a diverse range of functional groups. These results should be helpful to develop related transformations.

Experimental Section

Diisopropylethylamine (1 eq) was added to the suspension of precatalyst (20 mol%, 0.02 M) in toluene. The obtained mixture was stirred at room temperature for 10 min. Then the substrate was added and stirring was continued for 20 h. The solvent was evaporated and the residue was diluted with diethyl ether. The obtained suspension was filtered *via* a syringe filter and the solvent was evaporated.

Acknowledgements

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Highly Enantioselective, NHC-Catalyzed Intramolecular Annulations to Construct Benzo-Fused Pyranones with All-Carbon Quaternary Stereocenter

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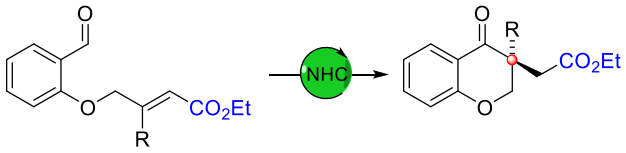

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