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2-Nitroallyl carbonate-based green bifunctional reagents for catalytic asymmetric annulation reactions†

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2-Nitroallylic carbonates, a new class of "green" 1,3-bielectrophilic reagents for organic synthesis and catalysis, have been prepared. The bifunctional tertiary amine-catalyzed asymmetric [3 + 3] annulations of cyclic enols with these reagents occur much faster than corresponding reactions with 2-nitroallylic esters and produce no acidic by-products poisoning the catalyst. Furthermore, 2-nitroallylic carbonates enable highly enantioselective one-pot synthesis of a variety of fused dihydropyrane derivatives from available precursors bearing pharmacophoric fragments.

Introduction

Asymmetric annulation reactions,[1] along with cycloaddition reactions,[2] are the most convenient and efficient methods for enantioselective synthesis of bi- and polycyclic organic compounds including natural compounds[3] that exhibit various biological activities.[4–11] These reactions allow a facile one-pot synthesis of densely functional molecules bearing several stereogenic centers from available bifunctional precursors.[1] A number of annulation cascades comprise asymmetric addition and cyclization steps. The latter may be accompanied by simultaneous cleavage of a leaving group,[12] such as the carbonate group, which is the most attractive from the "green chemistry" viewpoint.[13] The Morita–Baylis–Hillman (MBH) carbonates **I** are a classical example.[14,15] These bifunctional "green" reagents readily undergo the [3 + 2] annulation with electron-deficient olefins catalyzed by chiral amines or phosphines to afford pharmacology-relevant fused dihydropyrane derivatives, in particular, tetrahydropyrano[2,3-*e*]indoles,[16] benzo[*g*]chromene-5,10-diones,[17] tetrahydropyrano[2,3-*c*]pyrazoles,[18] chromanes and benzo[*f*]chromenes,[16] pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones,[19] bicyclo[3.3.1]nonan-9-ones[20] and tetrahydro-5*H*-pyrano[3,2-*c*]quinolin-5-ones[21] (Scheme 1). Carbon dioxide and an alcohol (Bu^tOH) are the only by-products in these reactions. The ester group-free allylic carbonates are widely used in allylation reactions.[22] 2-Nitroallylic alcohol derivatives (1,3-bielectrophilic nitro-MBH-reagents) **II** bearing easily transformable nitro group[23] are considered as suitable substrates for the ring-forming reactions. Unprotected nitroallylic alcohols (**IIa**)[24] and their acetates (**IIb**)[20,25–27] or 2-naphthoates (**IIc**)[21] enantioselectively react with cyclic enols to give dihydropyrane nitro derivatives through a [3 + 3] junction mode.[28,29] However, the reactions with unprotected 3-hydroxy-2-nitroalkenes **IIa** bearing a poor leaving group (LG = OH) require heating,[30] which may reduce selectivity. On the other hand, more active esters **IIb** and **IIc** inherently produce acetic or naphthoic acid by-products that poisoned a Lewis base catalyst and must be neutralized by addition of an external base.

We hypothesized that 2-nitroallyl carbonates **IId** that tended to release EtOH and CO_2 rather than harmful carbon acids would be preferable 1,3-bielectrophiles in these reactions (see Scheme 1). We expected that the absence of acidic by-products, incompatible with the catalyst, would eliminate the addition of an external base and allow performing the reaction with various cyclic enol precursors under mild conditions with high diastereo- and enantioselectivity. However, to our knowledge, 2-nitroallyl carbonates **IId** (LG = OC(O)OEt) have not been reported so far. Herein, we managed to synthesize these useful bifunctional reagents and successfully applied them in asymmetric catalytic annulations with cyclic 1,3-dicarbonyl compounds and their heterocyclic analogues.

Results and discussion

We synthesized 1,3-bielectrophilic nitro-MBH-reagents **2a–e** by careful treatment of the corresponding 2-nitroallylic alcohols[30]

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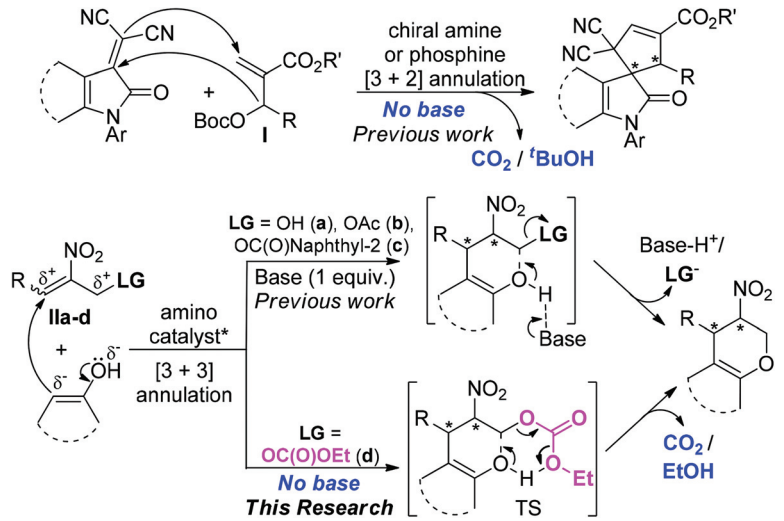
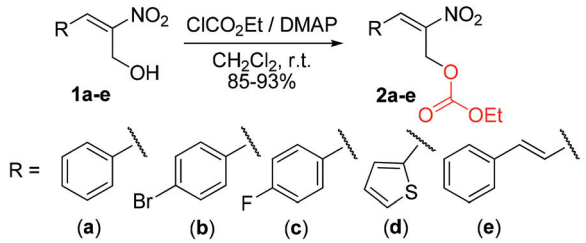


Scheme 1 Research strategy.



Scheme 2 Synthesis of 1,3-bielectrophilic nitro-MBH-reagents **2a–e**.

1a–e with ethyl chloroformate in the presence of a base (Scheme 2). Unexpectedly, the synthesis of these highly sensitive to bases small molecules appeared a challenging task. We examined various basic reagents and solvents in the alkoxycarbonylation reaction (see ESI†) and succeeded to synthesize the desired substrates **2a–e** as yellowish crystals in the high isolated yields (85–93%) using $ClCO_2Et$/DMAP in CH_2Cl_2 at ambient temperature.

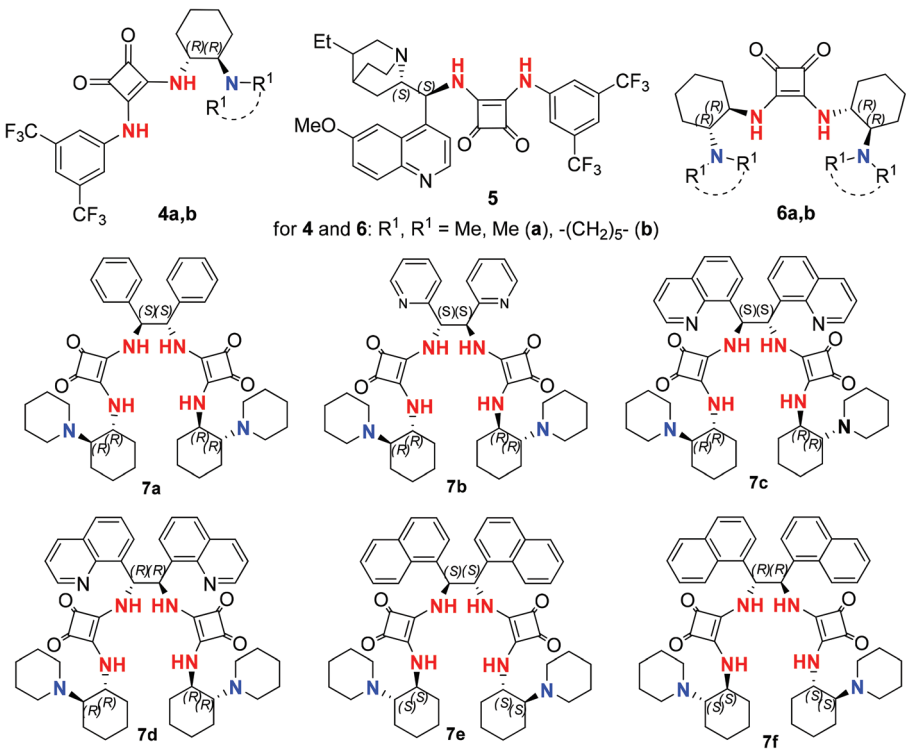
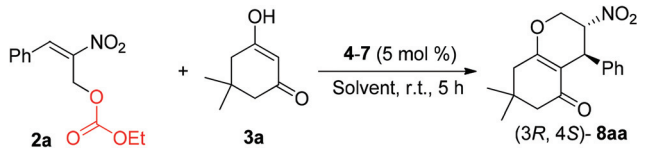


Fig. 1 Organocatalysts **4–7**.

Asymmetric annulation of 2-nitroallylic carbonate **2a** with dimedone **3a** served as a model reaction. At first, we studied this reaction in the presence of bifunctional tertiary amine-squaramides **4–7**, which proved to be efficient activators of carbon acids in reactions with electrophilic olefins (Fig. 1).[31–33]

In all the cases, product **8aa** was obtained in dichloromethane (DCM) in high isolated yields (80–99% over 5 h) with excellent diastereoselectivity (dr > 20 : 1) (Table 1, entries 1–11). However, enantioselectivities of the catalytic reactions depended on catalyst used. The best enantiomeric enrichment of **8aa** (94% ee) was observed in the reaction catalyzed by bifunctional Rawal-type tertiary amine **4b** (entry 2). Then, we examined the solvent effects on the outcome of the **4b**-catalyzed model reaction and found that THF, MeCN, and dichloroethane (DCE) provide inferior results (entries 12–14). In water, both the yield (72%) and stereoinduction (50% ee) were even worse (entry 15). Decreasing the catalyst loading to 0.5–1 mol% mitigated enantiomeric excess slightly but severely affected the reaction rate (entries 16 and 17). Importantly, the reaction in DCM appeared scalable at least 80-times, without affecting yield and selectivity (entry 18).

Table 1 Model reaction between **2a** and **3a** [a,b]



Entry	Cat	Solvent	Yield of **8aa** [c], %	ee[d], %
1	**4a**	DCM	90	75
2	**4b**	**DCM**	**96**	**94**
3	**5**	DCM	75	−82
4	**6a**	DCM	82	45
5	**6b**	DCM	80	86
6	**7a**	DCM	80	50
7	**7b**	DCM	85	55
8	**7c**	DCM	83	30
9	**7d**	DCM	81	47
10	**7e**	DCM	87	−68
11	**7f**	DCM	85	−80
12	**4b**	THF	94	89
13	**4b**	MeCN	92	88
14	**4b**	DCE	84	87
15	**4b**	H_2O	72	50 (56[e])
16[f]	**4b**	DCM	89	90
17[g]	**4b**	DCM	51	83
18[h]	**4b**	**DCM**	**93**	**92**

[a] Unless otherwise specified, the reaction conditions were as follows: **2a** (12.6 mg, 0.05 mmol), **3a** (7.0 mg, 0.05 mmol), catalysts **4–7** (5 mol%), solvent (0.1 mL). r.t. [b] Unless otherwise specified, dr was ≥20 : 1 for product **8aa** after flash-column chromatography on silicagel. [c] Yield after flash-column chromatography on silicagel. [d] HPLC data were obtained on the chiral phase (Chiralpak OD-H column, *n*-hexane/i-PrOH 90 : 10, flow rate 1.00 mL min^{-1}, 254 nm; $t_{R(major)}$ = 30.1 min, $t_{R(minor)}$ = 25.5 min). [e] dr 90 : 10, ee for *cis*-diastereomer is given in parenthesis. [f] The reaction was carried out with 1 mol% of catalyst **4b**. [g] The reaction was carried out with 0.5 mol% of catalyst **4b**. [h] The reaction was carried out with catalyst **4b** (97.4 mg, 0.2 mmol, 5 mol%), **2a** (1.00 g, 4.0 mmol) and **3a** (0.56 g, 4.0 mmol) in DCM (4.0 mL) for 7 h.

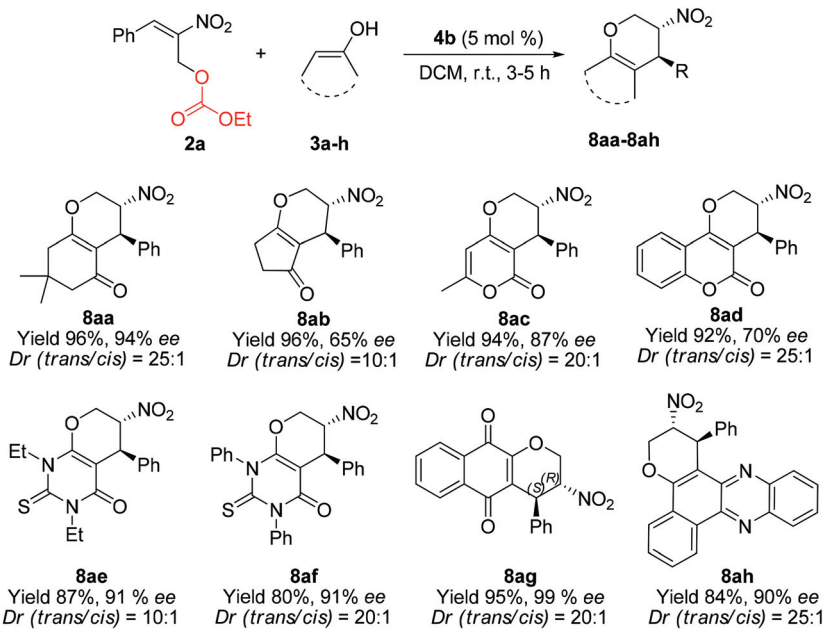
Under optimized conditions, cyclic enols **3b–h** reacted with 2-nitroallylic carbonate **2a** affording mainly *trans*-diastereomers (dr ≥ 10 : 1) of the corresponding fused dihydropyrane derivatives **8ab–8ah** in nearly quantitative yields (Scheme 3). Reactions of carbonate **2a** with cyclohexenone substrate **3a**, heterocycles **3e** and **3f** bearing the thiobarbiturate core, lawsone (**3g**) and benzo[*a*]phenazin-5-ol (**3h**) were characterized by high enantioselectivity (90–99% ee). Among tested substrates, lawsone (**3g**) exhibited the best reactivity and selectivity affording 98% of enantiomerically pure product **8ag** in 3 h time. The chiral induction was inferior for compounds **3b–d** containing fused cyclopentenone, pyranone and coumarin fragments (65–70% ee), while the excellent *trans*-diastereoselectivity was retained.

According to the X-ray diffraction data, compound **8ag** has the (3*R*,4*S*)-absolute configuration (Fig. 2). The (3*R*,4*S*)-configuration was assigned to other annulation products **8** by analogy.

2-Nitroallylic carbonates **2b–d** bearing halogenated aromatic ring or thiophene fragment bonded to the terminal olefinic carbon atom can be involved in the catalytic reactions with cyclic enols **3g** and **3h** (Scheme 4). Major *trans*-isomers of corresponding cross-annulation products **8bg**, **8ch** and **8dg** were stereoselectively assembled in these reactions in nearly quantitative yield with very high enantiomeric enrichment (92–99%). Interestingly, *trans*-diastereoselectivity in the reaction of carbonate **2b**, containing 4-bromopenyl group, with lawsone (**3g**) was noticeably lower than in similar reaction of thiophene-based nitroallylic carbonate **2d** (dr 5 : 1 *vs.* 25 : 1), while the enantioselectivity was superior in case of **2b** (97% *vs.* 92% ee). Nitrodiene **2e** also appeared suitable substrate for the annulation with lawsone (**3g**) to afford the styrene-derived heterocycle **8eg** as mainly *trans*-diastereomer with 99% ee.

The absolute configuration of stereogenic centers in products **8** is in accordance with the plausible transition state **TS$_1$**, in which the bifunctional tertiary amine-squaramide catalyst **4b** deprotonates cyclic enol **3** to produce active nucleophilic species (Scheme 5). Simultaneously, the same catalyst activates and appropriately orients in space nitroallylic substrate **2** through hydrogen bonding with the squaramide fragment to ensure high enantio- and diastereoselectivity of the catalytic process. The thus generated linear Michael adduct undergoes spontaneous intramolecular nucleophilic substitution accompanied by elimination of CO_2 and EtOH *via* the transition state **TS$_2$** to give fused dihydropyrane derivatives **8** as single diastereomer.

To compare activities of 2-nitroallylic carbonates and corresponding acetates in the catalytic annulations with cyclic enols, we undertook HPLC- and ^{1}H NMR-monitoring of the reactions between 4-hydroxycoumarin **3d** and carbonate **2a** or acetate **2a′** under similar conditions (**3d** (0.04 mmol), **2a** or **2a′** (0.04 mmol), **4b** (0.002 mmol, 5 mol%), DCM (1.0 mL), r.t.) (Fig. 3). The conversion in the reaction with carbonate **2a** after 15, 35, 65, 95, 155 and 200 min was an order of magnitude higher than that in the reaction with acetate **2a′**. The excellent activity of 2-nitroallylic carbonates **2a** in the catalytic reaction



Scheme 3 Variation of cyclic enols **3a–h**.

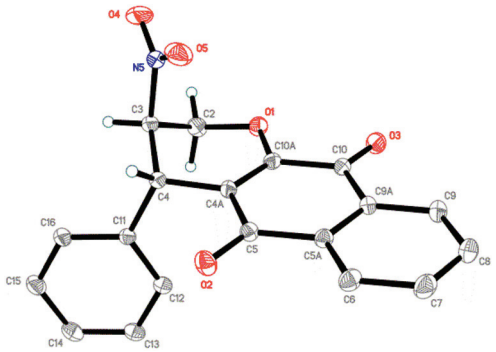
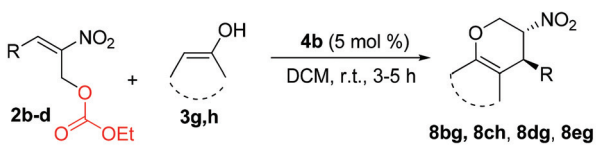
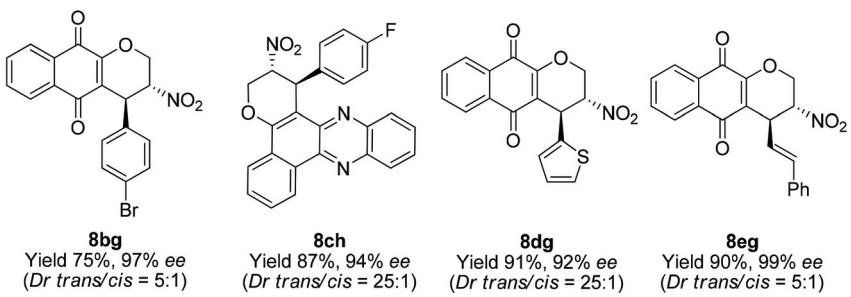


Fig. 2 X-ray data for **8ag**.

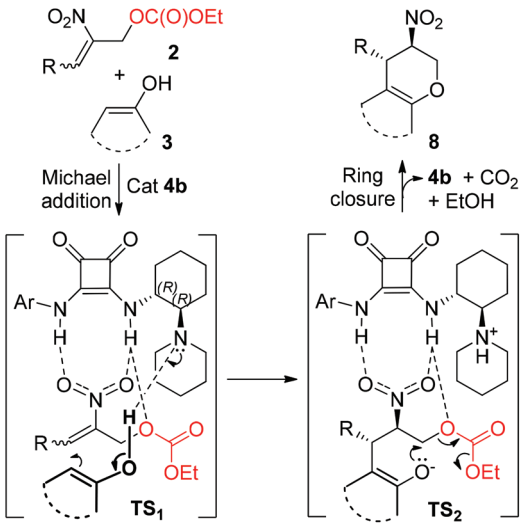
may be attributed to the maintenance the catalyst active sites over the catalytic process, in which irreversible protonation of the tertiary amino group does not occur, and to thermodynamic stability of the eliminating carbon dioxide.

The synthesized products **8** contain dihydropyrane structural unit that is present in herboxidiene[34,35] (antitumor activity) and zincophorin[36,37] (activity against Gram-positive bacteria) along with other useful heterocyclic motifs. Indeed, compound **8ac** incorporates 3,5-dihydroxysorbic acid δ-lactone, which is a precursor of sorbic, dienoic, and hexenoic acids. Dienoic acid is used to inhibit the growth of various molds and hexenoic acid and is applied as a flavoring agent.[38] Polycyclic product **8ad** contains masked 4-hydroxycoumarin





Scheme 4 Variation of 2-nitroallyl carbonates **2b–d**.



Scheme 5 Plausible reaction mechanism.

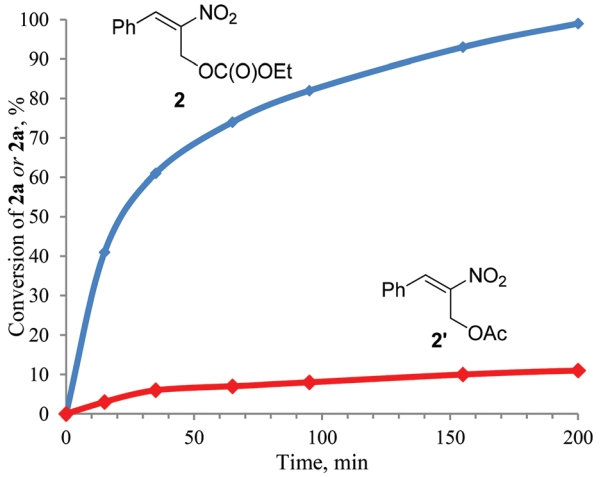


Fig. 3 Conversions of 2-nitroallylic carbonate **2a** and acetate **2a'** in the **4b**-catalyzed reactions with 4-hydroxycoumarin **3d**.

motif, which constitutes the structural core of anticoagulant warfarin.[39] Compounds **8ae** and **8af** belong to the barbiturate family of sedatives, hypnotics, and antioxidants.[40] Products **8ag**, **8bg**, **8dg** and **8eg** can be considered as derivatives of lawsone, the core structure of Atovaquone and dihydro-α-caryopterone which exhibit antimicrobial and anticancer activities.[41–43] Compounds **8ah** and **8ch** contain heterocyclic scaffold of benzo[*a*]phenazin-5-ol, a powerful anti-cancer agent sAJM589 (Fig. 4).[44]

Conclusion

In conclusion, we synthesized 2-nitroallylic carbonates that are the representatives of a new class of "green" reagents for asymmetric annulation reactions. These reagents exhibit much higher reactivity in the bifunctional tertiary amine-catalyzed asymmetric reactions with cyclic enols than the corresponding 2-nitroallylic acetates, and produce no acidic by-products deactivating the catalyst. In particular, they allow highly stereo- and enantioselective synthesis of fused dihydropyranes bearing pharmacology-relevant structural motifs and their analogues. The researches aimed at the extending application of 2-nitroallylic carbonates in organic synthesis and catalysis, are currently underway in our laboratory.

Author contributions

A.A. Kostenko – investigation; K.A. Bykova – investigation; A.S. Kucherenko – funding acquisition and methodology; A.N. Komogortsev – resources, B.V. Lichitsky – resources, S.G. Zlotin – conceptualization and supervision.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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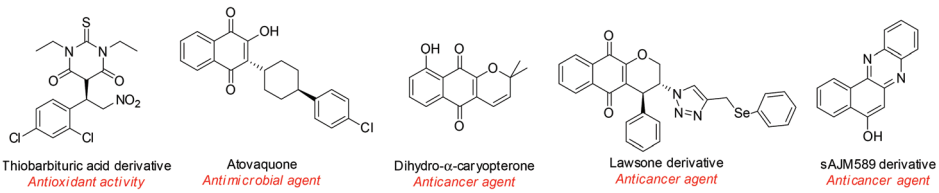

Fig. 4 Biologically active compounds containing barbiturate, lawsone, benzo[*a*]phenazine and dihydropyrane cores.

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