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Asymmetric Synthesis of β-Adrenergic Blockers through Multistep One-Pot Transformations Involving In Situ Chiral Organocatalyst Formation

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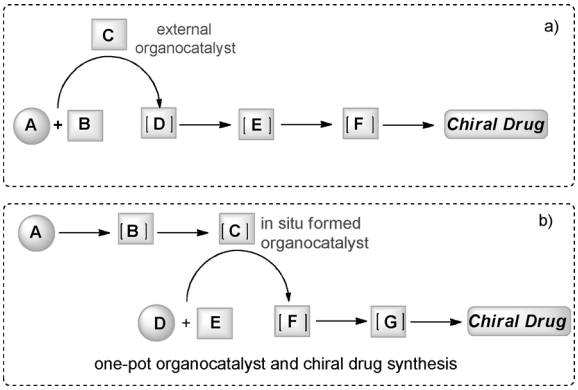
One-pot multistep operations involving organocatalysis are among the most recent, elegant, economically most attractive and sustainable methods in modern synthetic chemistry.[1] Whereas successful examples of one-pot organocatalytic methods[1,2] (and in particular those leading to chiral drugs or their intermediates[3]) rely on the use of organocatalysts synthesized in advance (Scheme 1a), to the best



Scheme 1. Depiction of the one-pot multistep sequential synthesis of chiral drugs involving an organocatalytic reaction step: a) using organocatalyst prepared in advance; b) by an in situ formed organocatalyst.

of our knowledge, no one-pot multistep drug synthesis involving an in situ multistep organocatalyst formation has been reported yet.

Whereas in metal-catalyzed reactions the in situ generation of chiral metal complexes is a rather common and established pathway,[4a–c] amongst the variety of asymmetric organocatalytic methods the involvement of in situ generated organocatalysts is still rare (e.g., one step formation of chiral carbenes from heterocyclic salts,[4d–g] dioxiranes from ketones,[4h–m] and 1,3,2-oxazaborolidines from amino alcohols[4n–q,5]).

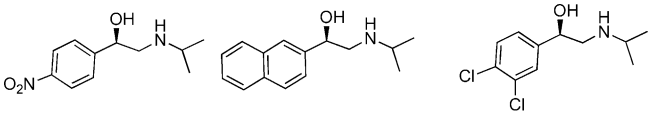
We envisioned that methods employing organocatalysts, prepared in situ through multistep one-pot transformations and used for the subsequent enantioselective multistep synthesis, might further contribute to the sustainability of the one-pot process through the additional reduction of work-up or purification steps (Scheme 1b). Herein, we disclose such a facile one-pot multistep synthetic approach applied directly to chiral drug synthesis.

To realize the idea presented in Scheme 1b, we have chosen 1,2-amino alcohols as attractive synthetic targets, which are of significant importance both in the pharmaceutical context and in nature.[6] Various asymmetric synthesis of these versatile compounds, for example, by the reduction–amination of α-tosyloxy and α-halo ketones,[7] the aminohydroxylation of olefins,[8] and by different other approaches,[9] have been reported. The enzymatic and catalytic reduction of α-amino ketones, as well as resolution of racemic 1,2-amino alcohols has also been demonstrated.[10]

However, isolation and purification of product intermediates is almost invariably tedious and difficult with most of these methods. Moreover, another drawback of some of these known procedures is the use of metal catalysts,[8,9a–d] which may be sources of chiral drug contamination as well as industrial pollution.

According to the suggested new approach (Scheme 1b), not only the target chiral drug but also the organocatalyst required for its enantioselective formation can be synthesized in a one-pot procedure without intermediate isolation or purification steps, therefore leading to the reduction of costs, saving materials, time and effort. We aimed to realize this one-pot strategy for the synthesis of selected β-adrenergic blockers **1**–**3** (Scheme 2). The pharmaceuticals nifenalol (**1**), pronethalol (**2**) and dichloroisoproterenol (**3**) are of great importance in the therapy of asthma, bronchitis, and congestive heart failure.[11]

The proposed five-step one-pot synthetic outline for the formation of target 1,2-amino alcohols is given in Scheme 3. We decided to carry out the in situ synthesis of chiral orga-



(*R*)-Nifenalol **1** (*R*)-Pronethalol **2** (*R*)-Dichloroisoproterenol **3**

Scheme 2. β-Adrenergic blockers with antianginal and antiarrhythmic properties.

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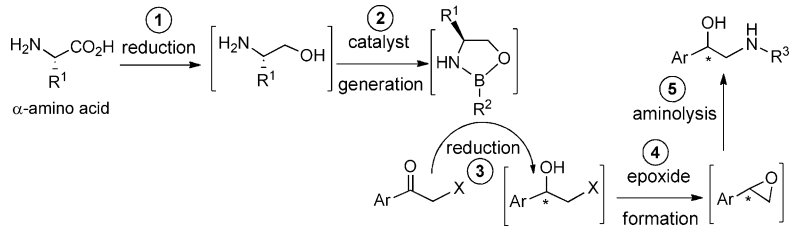


Scheme 3. Designed one-pot reaction sequence.

nocatalysts using α-amino acids as particularly attractive key starting compounds, justifying the requirements of ready availability and low costs.

Enantioselective 1,3,2-oxazaborolidine-catalyzed borane reduction of prochiral ketones to chiral secondary alcohols (see step 3, Scheme 3) is one of the most useful reactions in asymmetric synthesis.[4o,5] Amino alcohols **5a–c** are known as well suitable pre-catalysts for such Corey–Bakshi–Shibata (CBS)-type reduction of acetophenone.[12] L-Prolinol-derived 1,3,2-oxazaborolidine catalysts prepared from L-proline and giving the reduction product with moderate enantiomeric excess (*ee*) values were also studied.[13] Taking note of these reports we selected amino acids L-Leu (**4a**), L-Phe (**4b**), and L-Val (**4c**) with a primary amino functionality as starting compounds for realization of the proposed one-pot reaction sequence.

The first step is the amino alcohol formation through reduction of selected amino acids. Reductions of amino acids have been reported using lithium aluminium hydride,[14a] sodium borohydride,[14a,b] H_2 with Rh/Pt oxide (Nishimura catalyst),[14c] and BH_3-DMS (borane dimethyl sulfide complex) activated by BF_3-OEt_2 (boron trifluoride etherate).[14d] Since the first two methods are accompanied by the formation of trace impurities and partial racemization of the product, and Rh/Pt oxide catalyzed reaction is not suitable for the designed metal-free one-pot sequence, we selected the reduction employing borane for optimization of our first step.

After preliminary studies (see Table S1 of the Supporting Information) we found that the use of 1.5 equiv of borane reagent (relative to amino acid) and the reflux conditions were important to obtain good yields in this reduction reaction. It was further found that, whereas BH_3-DMS in toluene was the more appropriate system for the reduction of L-Leu and L-Phe (entries 3 and 6, Table 1), the combination of BH_3-THF in THF was much better suited for the reduction of L-Val (entry 7, Table 1). Notably, no racemization of amino alcohols **5a–c** under the selected reaction conditions was observed (see Table S2 in the Supporting Information).

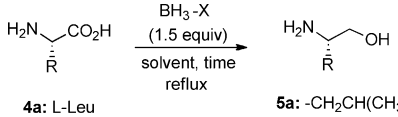
At the outset, improved conditions to those previously reported[14d] for the reduction of amino acids with borane were developed (entries 3, 6, and 7, Table 1) and applied in step 1 of our one-pot reaction.

It is known that combining separately optimized reactions (with isolation in each step) into a one-pot sequence does not guarantee the best outcome.[2] Moreover, the conditions found to be the best for individual reactions carried out with isolation are not necessarily well suited for one-pot sequential transformations. Hence, we decided to optimize the selected one-pot reaction sequence directly.

To find out the best suitable amino acid (among the selected ones **4a–c**) for the designed sequential transformation and to reach an efficient one-pot protocol for the synthesis of chiral drugs **1–3**, the three-step one-pot reaction sequence was next investigated under different conditions (Table 2). The in situ generation of chiral 1,3,2-oxazaborolidines **6a–c** and their subsequent application (without isolation) as catalysts for the reduction of acetophenone **7a** with BH_3-DMS at room temperature was selected as a model one-pot sequence. Variation of reducing agent, solvent and reaction time in step 1 and of reaction temperature in step 2 allowed us to make successful optimization of the one-pot process over three steps.

It was expected that B–OMe derivatives might perform better than the B-unsubstituted oxazaborolidines.[13,15] Notably, preliminary studies (see Table S3 in the Supporting Information) demonstrated that the use of 0.6 equiv of $B(OMe)_3$ (relative to the in situ generated amino alcohols **5a–c**, taking into consideration their theoretically possible yield from Table 1) was crucial to obtain good yield and enantioselectivity in the reduction of acetophenone. Therefore, B–OMe-derived oxazaborolidines **6a–c** were prepared in situ by addition of $B(OMe)_3$ (0.6 equiv) to **5a–c** and stirring for 1 h at the desired temperature (RT or 60 °C). Then, BH_3-DMS (1.2 equiv relative to **7a**) was added dropwise at room temperature within 1 h. Subsequently, acetophenone was slowly added over a 1 h period. A syringe pump was used for the addition of both reducing agent and reactant **7a**.

Table 1. Synthesis of precatalysts: amino alcohols **5a–c**.



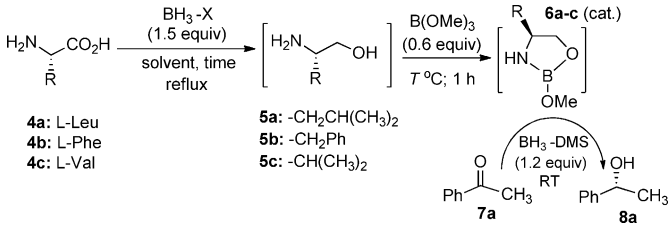
4a: L-Leu
4b: L-Phe
4c: L-Val

5a: -$CH_2CH(CH_3)_2$
5b: -CH_2Ph
5c: -$CH(CH_3)_2$

Entry	Amino acid	BH_3–**X**	Solvent	*t* [h]	Yield [%][a]
1	**4a**	THF	THF	17	56
2	**4a**	THF	THF	3	51
3	**4a**	DMS	toluene	3	79
4	**4b**	THF	THF	17	61
5	**4b**	THF	THF	3	65
6	**4b**	DMS	toluene	3	88
7	**4c**	THF	THF	17	<78
8	**4c**	DMS	toluene	3	<58
9	**4c**	DMS	THF	9	47
10	**4c**	THF	toluene	20	39

[a] Yields of isolated products. DMS = dimethyl sulfide.

Table 2. One-pot three-step sequential synthesis of chiral alcohols through in situ organocatalyst generation. Optimization of reaction conditions of steps 1 and 2 in a one-pot reaction.



Entry	Step 1 Amino acid	X	Solvent	t [h]	Step 2 T [°C]	Yield [%][a]	ee [%][b,c]
1	**4a**	DMS	toluene	3	RT	>99	24
2	**4a**	DMS	toluene	3	60	>99	21
3	**4a**	THF	THF	3	60	>99	59
4	**4b**	DMS	toluene	3	RT	>99	16
5	**4b**	DMS	toluene	3	60	>99	17
6	**4b**	THF	THF	3	60	>99	62
7	**4c**	THF	THF	17	RT	>99	80
8	**4c**	DMS	Toluene	3	60	>99	33

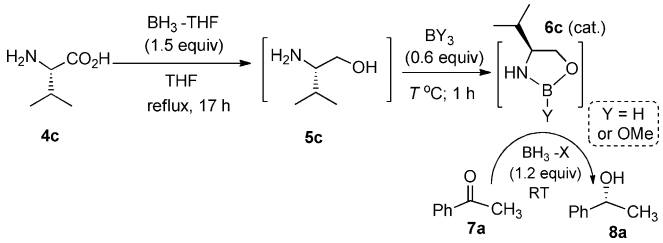
[a] Yields of isolated products. [b] Determined by chiral phase HPLC analysis and compared to authentic racemic material. [c] The absolute configuration at the stereocenter was established by comparison with literature data (see Table S4 in the Supporting Information).

The in situ generated catalysts **6a–c** were applied at $\leq$20 mol% loading relative to **7a** (theoretically calculated, taking into consideration the expected yields for **5a–c** given in Table 1).

The conditions found in entry 7 of Table 2 (with L-Val as a starting amino acid, BH_3-THF as a reducing agent and THF as a solvent) giving the product **8a** in over 99% yield and 80% *ee* using the in situ formed catalyst **6c** were selected for further studies.

Next, the conditions of the in situ synthesis of CBS-type catalyst **6c** (step 2, Table 3) and the subsequent reduction of ketone **7a** (step 3, Table 3) were further optimized. In particular, the "additive" BY_3 and reaction temperature in step 2 as well as the reducing agent BH_3-X (BH_3-DMS vs. BH_3-THF) in step 3 have been varied (Table 3).

Table 3. Optimization of reaction conditions of steps 2 and 3.

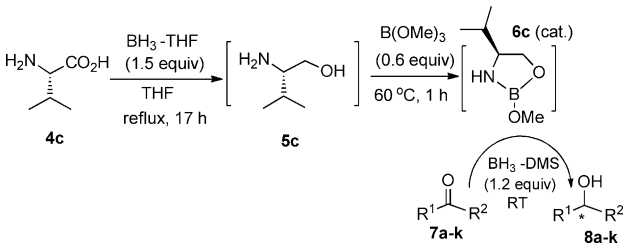


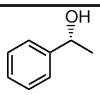
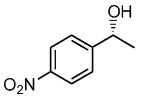
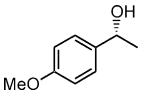
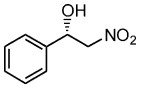
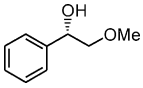
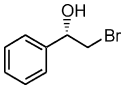
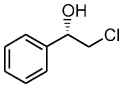
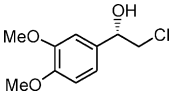
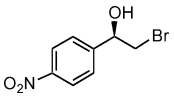
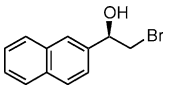
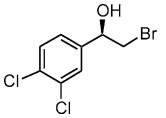
Entry	Step 2 BY_3	T [°C]	Step 3 X	Yield [%][a]	ee [%][b]
1	$B(OMe)_3$	RT	DMS	>99	80
2	$B(OMe)_3$	RT	THF	>99	31
3	BH_3-DMS	RT	DMS	>99	80
4	BH_3-THF	RT	DMS	>99	77
5	BH_3-THF	60	DMS	>99	78
6	$B(OMe)_3$	60	DMS	>99	87

[a] Yields of isolated products. [b] Determined by chiral phase HPLC analysis and compared with authentic racemic material.

Our studies revealed that the use of $B(OMe)_3$ as an "additive" at 60°C for in situ catalyst synthesis (step 2, Table 3), and of BH_3-DMS as a reducing agent in step 3 had a pro-

Table 4. Scope of the reaction.



Entry	Product		Yield [%][a]	ee [%][b,c]
1		**8a**	>99	87
2		**8b**	>99	71
3		**8c**	98	72
4		**8d**	>99	77
5		**8e**	>99	81
6		**8f**	>99	90
7		**8g**	>99	94
8		**8h**	>99	91
9[d]		**8i**	>99	88
10[d]		**8j**	>99	92
11[d]		**8k**	>99	nd[e] $[\alpha]_D^{20}=-30.7$ (c=1.0, $CHCl_3$)

[a] Yields of isolated products. [b] Determined by chiral phase HPLC analysis and compared with authentic racemic material. [c] The absolute configuration at the stereocenter was established by comparison of the sign of specific rotations with the literature values (see Table S4 in the Supporting Information). [d] D-Val was used for the in situ synthesis of the catalyst. [e] Not determined because no appropriate conditions for chiral phase HPLC analysis were found for **8k**.

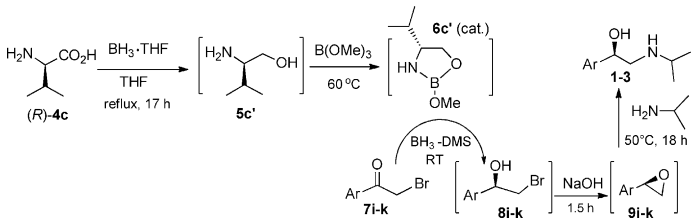
nounced effect on the resultant enantioselectivity of the reaction product **8a** (entry 6 vs. entries 1–5, Table 3).

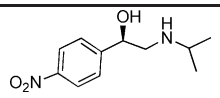
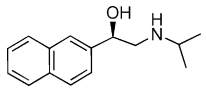
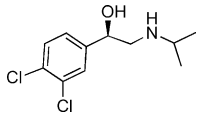
Motivated by this result, we next examined the scope of the developed one-pot process for different prochiral ketones using the optimized reaction conditions. The results are summarized in Table 4. To our delight, all the reactions investigated can be effected in excellent yields (98–99%) and with good to high enantioselectivities (71–94%). Generally, higher enantioselectivities were obtained using α-halo ketones (Table 4, entries 6–10).

Consequently, the anticipated one-pot sequential transformations leading to selected chiral drugs **1–3** was successfully attempted (for optimization of epoxidation and aminolysis reaction steps; see Tables S5 and S6 in the Supporting Information). Whereas L-Val gave the *S*-configured products (see Table S7 of the Supporting Information), application of D-Val as a starting amino acid gratifyingly gave the desired *R*-configured products **1–3** with good yields and excellent enantioselectivities (96–99% *ee*, entries 1–3, Table 5).

Whereas the individual reactions selected for realization of our one-pot synthesis (e.g., reduction, epoxide formation and aminolysis) are already known,[16] the combination of these transformations with an in situ organocatalyst generation in a one-pot sequential multistep process leading to chiral drugs is unprecedented.

Table 5. One-pot sequential synthesis of β-blockers **1–3** by in situ organocatalyst generation.



Entry	Product		Yield [%][a]	*ee* [%][b]
1		**1**	82	96
2		**2**	78	98
3		**3**	80	99

[a] Yields of isolated products. [b] Determined by chiral phase HPLC analysis and compared to authentic racemic material.

In conclusion, we have demonstrated here a new one-pot approach to enantioselective synthesis, involving in situ organocatalyst formation (from commercially available and inexpensive starting materials, for example, amino acids) and the application of the reaction for further multistep sequential synthesis. This obviates the need of work-up and purification steps not only for the synthesis of target compounds, but also those required for the synthesis of external organocatalyst, leading to the further reduction of costs, materials and labor input and making the one-pot synthetic strategy even more efficient, atom economical and environmentally friendly.

The application of this facile and straightforward method to the synthesis of important chiral drugs, β-adrenergic blockers **1–3**, has been successfully demonstrated. Further efforts to evaluate the scope of the related processes are underway.

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Keywords: amino alcohols · asymmetric synthesis · drug synthesis · one-pot reactions · organocatalysis · reduction

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