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COMMUNICATION

Efficient Synthesis of 2-Amino-1-Arylethanols Through a Lewis Base-Catalyzed $SiCl_4$-Mediated Asymmetric Passerini-Type Reaction

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Abstract: We herein report, a practical and efficient strategy for the synthesis of enantiomerically enriched 2-amino-1-arylethanols, a structural motif commonly encountered in the family of β-adrenergic blockers or agonists, through a Lewis base-catalyzed $SiCl_4$-mediated asymmetric Passerini-type reaction of isocyanides with aldehydes. The protocol features a simple one-pot, two-step procedure, the use of commercially available starting materials, a broad functional group tolerance and high levels of selectivity up to 98.5:1.5 er. Application to the synthesis of the salbutamol acetate salt, a drug widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases is also reported.

Enantiomerically pure 1,2-amino alcohols are highly valuable scaffolds that, besides their wide applications in organic synthesis both as chiral ligands and auxiliaries, are found in many naturally occurring compounds and pharmacologically relevant molecules.[1] In particular, 2-amino-1-arylethanols that belong to the family of β-adrenergic blocking or activating agents, are a group of molecules that inhibits or activates β-adrenergic receptors. They are widely prescribed in the therapy of asthma, bronchitis, and congestive heart failure. Representative examples of this class of efficient drugs are depicted in Figure 1. Timolol[2] is a non-selective β_1-adrenergic antagonist used for the treatment of glaucoma and ocular hypertension. Salbutamol,[3] also known as albuterol and marketed as Ventolin® is one of the oldest selective β_2-adrenoreceptor stimulants with a rapid and potent bronchodilator activity intensively used to treat asthma, while Bambuterol[4] and Clenbuterol[5] are two selective long-acting bronchodilators with distinct mechanisms, generally prescribed for their extended durations of action.

Given the high medicinal value of 2-amino-1-arylethanols, it is not surprising, therefore, that the development of truly efficient methods for their preparation in enantiomerically pure or enriched forms has been explored and still remains a paramount goal of practical significance in both academia and industry.[6] To date, current stereoselective approaches rely on addition-type reactions that include either functional group manipulations of vicinal *N*,*O*-compounds such as diastereoselective nucleophilic additions[7] and asymmetric reductions of imines and ketones,[8] or addition of *N*/*O*-compounds on suitable substrates such as ring-opening of epoxides[9] and aziridines,[10] as well as oxyamination reactions.[11] It has been also established that optically active nitroaldol or cyanohydrin adducts obtained from the corresponding benzaldehydes can lead to the 2-amino-1-arylethanols.[12] Reductive cross-coupling reactions of imines with carbonyl derivatives have also been developed.[13] However, although efficient, most of these methods suffer from some disadvantages such as the need of stoichiometric amounts of chiral reducing agent or auxiliary, the use of expensive noble metal catalysts, stereochemistry issues along with structurally limited substrates/products and multiple synthetic steps that often require tedious purifications. Consequently, there is still much room for the development of more sustainable and straightforward protocols for the synthesis of 2-amino-1-arylethanols with high levels of chemical efficiency and stereocontrol.

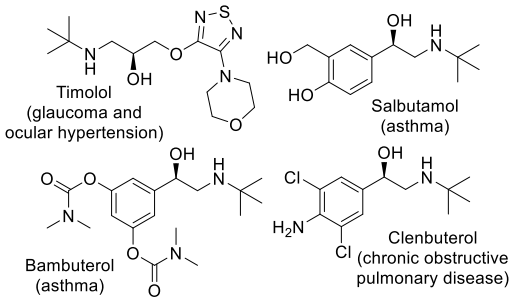

Figure 1. Representative 2-Amino-1-Arylethanol Drugs.

As part of our ongoing research program dedicated to the design and synthesis of new chiral diphosphine dioxide ligands and their applications[14,15] as chiral Lewis bases for asymmetric catalysis,[16] we report in this contribution a practical and efficient new one-pot, two-step strategy for the preparation of optically active 2-amino-1-arylethanols through a Lewis base-catalyzed $SiCl_4$-mediated cascade process. This protocol involves a Passerini-like reaction between various aldehydes and isocyanides,[17] that furnished not "truncated" Passerini

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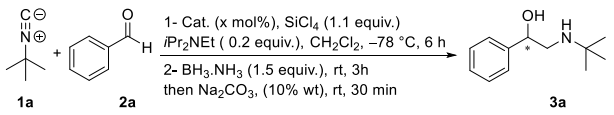
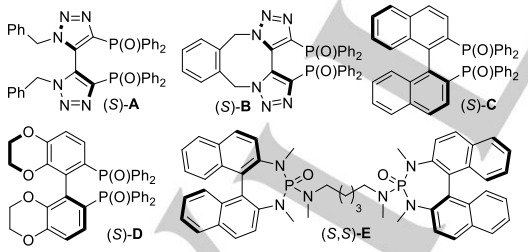
compounds but 2-aminoalcohols instead, *via* subsequent *in situ* reduction of the resulting α-trichlorosilyloxyimidoyl chloride intermediates.[18] Notably, our approach even enables the facile introduction of a bulky *tert*-butyl group attached to the nitrogen atom, that besides being a common feature of a broad range of β-adrenergic medicines as highlighted in Figure 1, has proven to be an essential structural feature for achieving high selectivity for a specific β-adrenergic receptor and provides better stability against unwanted metabolic *N*-dealkylation reaction.[19]

We began our investigation by searching the most efficient chiral Lewis base catalysts to perform the asymmetric α-addition of *t*Bu-isocyanide **1a** to benzaldehyde **2a**, which resulted in the formation of 2-(*tert*-butylamino)-1-phenylethan-1-ol **3a**.

Table 1. Optimization of Reaction Conditions[a]



Entry	Cat./mol%	Solvent	Conv. [%][b]	Yield [%)][c]	er [%][d]
1[e]	**A**/5	CH_2Cl_2	100	69	63:37
2[e]	**B**/5	CH_2Cl_2	100	62	54:46
3[e]	**C**/5	CH_2Cl_2	100	61	58:42
4[e]	**D**/5	CH_2Cl_2	100	70	52:48
5[e]	**E**/5	CH_2Cl_2	100	73	90:10
6[e]	**E**/5	DCE	80	58	81:19
7[e]	**E**/5	EtCN	90	60	85:15
8[e]	**E**/5	toluene	44	26	nd
9[e]	**E**/5	THF	49	29	nd
10[f]	**E**/5	CH_2Cl_2	100	61	97:3
11[f]	**E**/3	CH_2Cl_2	100	77	96:4
12[f]	**E**/1	CH_2Cl_2	100	62	89:11



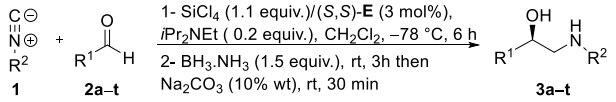
[a] Reaction performed at –78 °C using x mol % of catalyst with PhCHO (1 mmol), *t*BuNC (1.2 mmol), $SiCl_4$ (1.1 mmol 1M in CH_2Cl_2) and iPr_2NEt (0.2 mmol) in 1 mL of solvent for 6 h. [b] Determined by ^1H NMR. [c] Yields. [d] Determined by HPLC. The absolute configuration was determined to be *R* by comparing the sign of the specific rotation with the literature data. [e] Dropwise addition of *t*BuNC in CH_2Cl_2 over 15 min. [f] Dropwise addition of *t*BuNC in CH_2Cl_2 over 4 h.

Toward this end, several Lewis base organocatalysts (**A**–**E**) were screened. Initial experiments were carried out in dichloromethane at – 78 °C, with a dropwise addition of *t*Bu-isocyanide over a period of 15 min using a combination of 5 mol % of catalyst with 1.1 equivalent of $SiCl_4$ and a catalytic amount of diisopropylethylamine for 6 h. As depicted in Table 1, the reaction proceeded smoothly to give the desired amino alcohol **3a** with complete conversion for all Lewis base catalysts examined. However, both the chemical yields and enantiomeric ratios were greatly affected by the structure of the catalysts (entries 1−5). For instance, reactions conducted with the "home-made" bis-(triazolyl)diphenylphosphine dioxide catalysts **A** and **B** delivered the desired 2-(*tert*-butylamino)-1-phenylethan-1-ol **3a** in acceptable yields of 69% and 62%, but with disappointing enantiomeric ratios of 63:37 and 54:46, respectively (entries 1 and 2). Comparable results were achieved with atropisomeric (*S*)-BINAPO **C** and (*S*)-SYNPHOSO **D** ligands. Gratifyingly, very promising results were obtained from Denmark's doubly atropisomeric bis-phosphoramide catalyst **E**, a highly efficient chiral Lewis base that have found widespread applications in promoting various stereoselective transformations, giving **3a** in 73% isolated yield and with a good enantiomeric ratio of 90:10. A rapid solvent screening revealed that dichloromethane was ideal in view of the chemical efficiency and stereocontrol (entries 6−9). In addition, we found that the enantiomeric ratio is significantly improved by preventing the non-selective pathway through the slow addition of *t*Bu-isocyanide over 4 h (entry 10). Further attempts to increase the selectivity of the process by lowering the catalyst loading did not meet with success. Indeed, reaction performed with 3 mol % of bis-phosphoramide catalyst **E** furnished compound **3a** with an enantiomeric ratio similar to that reported for 5 mol %, while a marked drop in the selectivity was observed when using only 1 mol % of organocatalyst **E**. This result suggested that lowering the catalyst loading presumably slowed down the enantioselective pathway by decreasing the concentration of the *in situ* generated reactive chiral hypervalent silicate intermediate, thus favoring the non-selective reaction induced by $SiCl_4$ itself (entries 11−12).

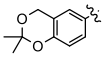
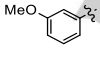
With the optimized reaction conditions in hand, we next explored the substrate scope of this Lewis base-catalyzed $SiCl_4$-mediated asymmetric Passerini-type reaction. As shown in Table 2, good yields and high levels of asymmetric induction up to 98.5:1.5 er were generally obtained for all aromatic aldehyde substrates probed with a significant structural variation. We observed that both reactivity and enantioselectivity highly depended on the position and electronic nature of the R^1 substituent attached to the aryl ring. For instance, α-addition of *t*Bu-isocyanate **1a** to benzaldehyde derivatives **2a**–**t** that bear electron-withdrawing groups such as $–CF_3$ or –Br at the para position resulted in the formation of the corresponding 2-amino-1-arylethanols **3b** and **3c** in 73% and 76% yields and with high enantiomeric ratios of 96.5:3.5 and 6.5:93.5, respectively (entries 2 and 3). Comparable high catalytic activity was achieved with para substituted aldehydes having electron donating groups such as –Me and $–OC(Me)_2OCH_2$-, giving aminoalcohols **3d** and **3f** in 75% and 71% yields and excellent stereocontrol with 98.5:1.5 and 98:2 er, respectively (entries 4 and 6). Notably, and for unclear reasons, the reaction performed with *p*-MeO anisaldehyde **3e** led to a slightly lower selectivity of 91:9 er, albeit with a similarly good yield of 75% (entry 5). The catalytic efficiency is restored when the reaction is carried out with meta-substituted arylaldehydes possessing electron-donating groups, providing products **3g**−**i** with enantiomeric ratios between 92:8 and 96:4 and isolated yields varying from 73 to 77% (entries 7–9). In contrast, the presence of electron-withdrawing substituents such as –Br or $–CF_3$ at the meta position resulted in the formation of **3j** and **3k** in high chemical yields but with a significant decline in the observed selectivity with 86:14 and 84.5:13.5 er, respectively (entries 10 and 11). Interestingly, steric hindrance of the substrates does not affect the outcome of the catalysis, in particular for ortho-substituted aldehydes. Indeed, compounds **3l** and **3m** with either

an electron-withdrawing Cl-group or an electron-donating Me-group, were generated in good yields and with excellent enantiomeric ratios of 96:4 and 97.5:2.5, respectively (entries 12 and 13). The same trend was observed when sterically hindered 1-naphthaldehyde was used, giving **3n** in 70% yield with an excellent er of 96.5:3.5, whereas the reaction performed with the less hindered 2-naphthaldehyde delivered product **3o** in 80% yield and a marked decrease in the selectivity with an enantiomeric ratio of 87:13 (entries 14 and 15). Notably, alkyl substituted aldehydes proved to be suitable partners for this process, affording the corresponding adducts 3**p** and **3q** in 68% and 72 % yields and with good enantiofacial discrimination of 91.5:8.5 and 9:91, respectively (entries 16 and 17). Moreover, it turned out that the reaction proceeded likewise with substrate having a thienyl group, although a significant drop in the catalytic activity was observed in this case, giving **3r** in 72% yields and a disappointing enantiomeric ratio of 75:25 (entry 18). Finally, the nature of the isocyanide on the catalytic activity was briefly studied. As illustrated in Table 2, *i*Pr-isocyanide is not a good partner in this reaction providing low reactivity, while the use of Cy-isocyanide gave the desired 2-amino-1-arylethanol **3t** with a marked decrease of both yield and selectivity compared to the result obtained with *t*Bu-isocyanide (entries 19 and 20).

Table 2. Amino Alcohol Syntheses: Substrate Scope[a]

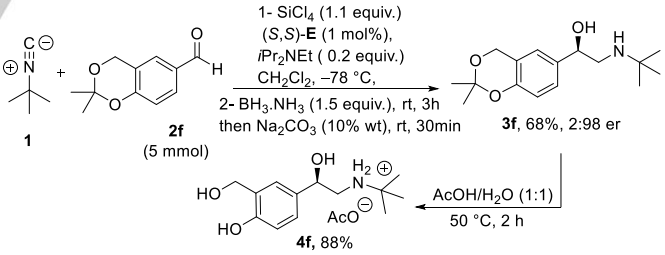


1 **2a–t** **3a–t**

Entry		R^1	R^2	Yield [%)][b]	er [%][c]
1	**3a**		*t*Bu	77	96:4
2	**3b**		*t*Bu	73	96.5:3.5
3	**3c**		*t*Bu	76	6.5:93.5
4	**3d**		*t*Bu	75	98.5:1.5
5	**3e**		*t*Bu	75	91:9
6	**3f**		*t*Bu	71	2:98
7	**3g**		*t*Bu	73	93.5:6.5
8	**3h**		*t*Bu	74	92:8
9	**3i**		*t*Bu	77	96:4
10	**3j**		*t*Bu	80	86:14
11	**3k**		*t*Bu	78	84.5:14.5
12	**3l**		*t*Bu	70	96:4
13	**3m**		*t*Bu	71	97.5:2.5
14	**3n**		*t*Bu	70	96.5:3.5
15	**3o**		*t*Bu	79	87:13
16	**3p**		*t*Bu	68	91.5:8.5
17	**3q**		*t*Bu	72	9:91
18	**3r**		*t*Bu	72	75:25
19	**3s**		*i*Pr	36	nd
20	**3t**		Cy	53	62.5:37.5

[a] Reaction performed at –78 °C in CH_2Cl_2 using 3 mol % of (*S*,*S*)-**E** with various aldehydes (1 mmol), $SiCl_4$ (1.1 mmol 1M in CH_2Cl_2), iPr_2NEt (0.2 mmol) in 1 mL of CH_2Cl_2 and with a dropwise addition of a CH_2Cl_2 solution of isocyanides over 4 h (1.2 mmol). [b] Yields. [c] Determined by HPLC.

Interestingly, scale-up of the reaction at lower catalyst loading of 1 mol% occurred without problems. For instance, a five-fold scale-up at 5 mmol (≃ 1 g) of the acetonide protected aldehyde **2f** gave the optically enriched key intermediate of salbutamol **3f** in 68% yield without erosion of the enantioselectivity (up to 2:98 er). To avoid racemization, deprotection of the isopropylidine ketal moiety was performed under mild aqueous acidic conditions, leading to the antiasthmatic drug (*R*)-salbutamol acetate salt **4f** in 88% yield with ^1H and ^{13}C NMR spectral as well as specific rotation data in full agreement with those reported in the literature (Scheme 1).[18,20] This result clearly underlines the practicality and the usefulness of the herein reported protocol to access medicinally valuable chiral 2-amino-1-arylethanols.



Scheme 1. Scale-up Synthesis of (*R*)-Salbutamol Acetate **4f**.

To conclude, we reported an atom economical and attractive route to pharmaceutically relevant 2-amino-1-arylethanols through Lewis base-catalyzed $SiCl_4$-mediated cascade procedure. This metal-free, one-pot two-step process has some attractive features such as the use of commercially available starting materials, operational simplicity, a broad functional group tolerance and high levels of selectivity up to 98.5:1.5. Moreover, we demonstrated the effectiveness and scalability of our approach through the gram-scale preparation of the Salbutamol acetate salt, a drug widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Passerini Reaction • 2-Amino-1-arylethanols • Asymmetric Catalysis • Lewis Base • Salbutamol

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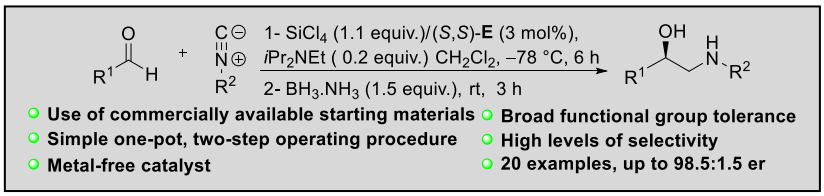
Organocatalysis



An atom economical and metal-free, one-pot two-step asymmetric synthesis of highly valuable 2-amino-1-arylethanols has been established from commercially available starting materials. The effectiveness and scalability of our approach has been demonstrated via the synthesis of the Salbutamol acetate salt, a bronchodilator widely used to treat asthma.