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An entry to non-racemic β-tertiary-β-amino alcohols, building blocks for the synthesis of aziridine, piperazine, and morpholine scaffolds†

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A method for the preparation of enantiopure β-*tert*-amino alcohols bearing a tetrasubstituted *C*-stereocenter, as well as their conversion into selected medicinally privileged heterocyclic systems (morpholines, aziridines, piperazines) is reported. These compounds were obtained through enantiospecific sigmatropic rearrangement of allyl carbamates as a key step. The latter were prepared from the corresponding β,β′-dialkyl-substituted non-racemic allyl alcohols. In addition, an asymmetric synthesis of such highly substituted allylic alcohols *via* either enantioselective 1,2-reduction of enones, enzymatic kinetic resolution, or a functionalization of chiral propargyl alcohols, with discussion of scope and limitations of each method is reported.

Introduction

The 1,2-amino alcohol unit is an important structural motif in various natural products, medicinally active compounds, chiral auxiliaries, and privileged ligands. Nowadays, over 300 000 compounds containing this unit are known, including more than 2000 natural products, almost 100 FDA-approved drugs, and hundreds of drug candidates.[1,2] The formation of these structures has therefore received widespread attention from the synthetic organic chemistry community (Scheme 1).[1,2]

The synthesis of such compounds has stimulated continuing interest and extensive efforts (Scheme 1).[1–12] Standard methods for the synthesis of enantiopure vicinal amino alcohols involve various addition reactions which mostly require non-racemic substrates or reagents (Scheme 1). Most common strategies are based on functional group transformation of vicinal *N*,*O*-compounds (*e.g.* reduction of natural amino acids),[4–6] addition of *N*/*O*-heteroatoms to substrates,[3,8–10,12] and transformation of nitro aldol (Henry) reaction products.[11,13] These strategies, including their catalytic enantioselective variations, suffer from either structurally limited substrates/products or relatively low regio- and stereoselectivity. Difficulties in the control of regioselectivity are also an issue in the ring opening of aziridines and epoxides.

Recently, several radical cross-coupling strategies between amine and alcohol moieties have been reported.[7] Among them, protocols involving SmI_2-mediated reductive cross-coupling of imine derivatives[11,14,15] or nitrones[16–19] with aldehydes or ketones have been developed. Unfortunately, the use of stoichiometric amounts of SmI_2 as reductant is a substantial limitation and challenge for enantioselective variants with the use of chiral ligands.[11,20] An additional disadvantage are the unavoidable side-reactions (*e.g.* pinacol-type homocoupling or reduction of substrates). An interesting alternative are visible light-mediated transformations,[21–28] although there are only a few reports on enantioselective protocols involving photocatalyst-merged dual catalyst systems with chiral phosphoric acid organocatalyst[21] or chiral rhodium Lewis acid,[23] or bifunctional Lewis acid/photoredox catalyst[24] of chiral-at-metal iridium complex.[22] In 2018, Huang and co-workers[25] reported the reductive cross-coupling reaction of aldononitrones with aromatic aldehydes *via* the synergistic catalysis of Ru-photocatalyst and chiral $Sc(OTf)_3$/*N*,*N*′-dioxide complex. The reaction proceeded also for ketonitrones, but only ketonitrones derived from symmetric ketones were tested. Nevertheless, all of the mentioned methods relied heavily on specially designed substrates.

None of the above fit perfectly for a synthesis of type **1** enantiopure vicinal amino alcohols (Scheme 2). Their synthesis through functional group transformation requires an access to enantiopure quaternary amino acids or aziridines, whose preparation in enantiopure form is a challenging task in itself. Also, the synthesis of **1** by radical coupling can be problematic since the generation of formaldehyde-derived radical species is not straightforward. The use of formaldehyde as a reagent for such a process, as well as others processes, *e.g.* the

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†Electronic supplementary information (ESI) available: Experimental procedures, characterization of organic compounds, copies of ^1H, ^{13}C spectra and HPLC data for selected compounds. See DOI: 10.1039/d0ob01315c

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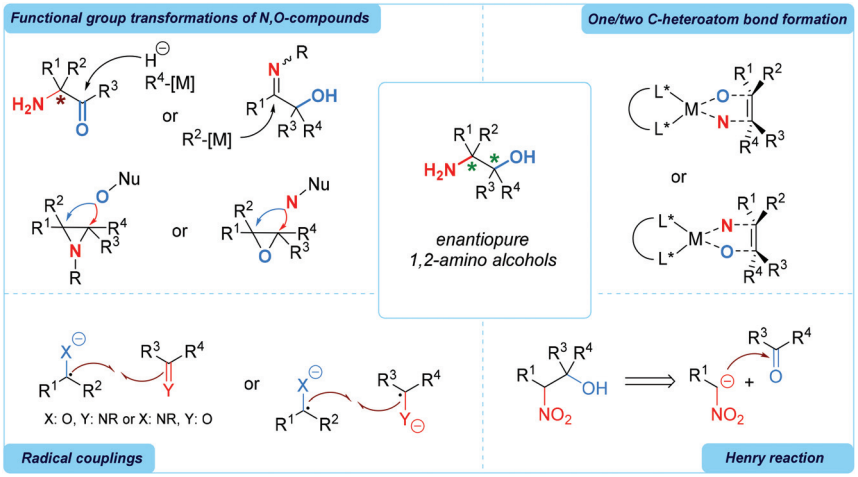
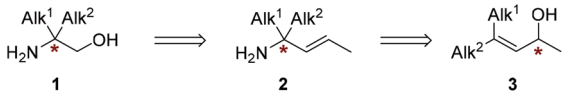


Scheme 1



Scheme 2

Henry reaction, is problematic from the stereochemical point of view, since very often for these transformation, the carbonyl partner is a significant contributor of asymmetric induction at the transition state. For such a small and achiral reagent, the developed protocols have to involve complex chiral systems to provide sufficient levels of enantioselectivity.

Therefore, establishing a protocol for direct and efficient preparation of enantiopure amino alcohols **1** is still required. We sought to investigate the preparation of **1** through [3,3]-sigmatropic rearrangement of allyl alcohols to **2** derivatives. In general, sigmatropic rearrangements are an excellent tool for the creation of stereogenic centers, particularly those of high steric hindrance.[29–31] The reason for that is the intramolecular course of the process and its concerted mechanism. In consequence, these reactions allow for highly stereoselective generation of stereogenic centers through chirality transfer along the allylic system.

Results and discussion

In order to investigate the feasibility of this proposal, in the initial attempt, we began with the synthesis of β,β-dialkyl substituted allyl alcohols **3**. The synthesis of enantiopure type **3** alcohols is rather challenging and only a few examples, including enzymatic[32] and catalytic[33] kinetic resolution of racemates, addition of organometallics to chiral aldehydes[34] or sequential functionalization of enantiopure propargyl alcohols,[35–37] are known. We decided to prepare these compounds through a less explored enantioselective 1,2-reduction[38–42] of the corresponding enones **6**. The latter were prepared through a 1,4-addition reaction of organocopper reagents to alkynes **4**. The addition reaction provided α,β-unsaturated esters **5** as single isomers in most cases (Table 1). Then, esters **5** were readily converted into Weinreb amides which, upon treatment with MeMgBr, gave the corresponding unsaturated ketones **6**. As mentioned, the 1,4-addition step provided mainly single isomers (*E* or *Z*). In a few cases, slight contamination with the other isomer was readily removed through column chromatography of the corresponding Weinreb amides.

With a series of β,β-disubstituted enones **6** in hand, studies on their enantioselective reduction were conducted. The CBS reduction of model enone **6a** with $BH_3{\cdot}Me_2S$ in the presence of a chiral (*S*)-(−)-Me-oxazaborolidine (Scheme 3, Method A) provided the corresponding alcohol **(*R*)-3a** with good yield (87%) and moderate enantioselectivity (79% ee).[43] The Cu-catalyzed hydrosilylation (Scheme 3, Method B), which we have successfully utilized in the past,[36] proceeded efficiently, but the level of enantioselectivity was still insufficient. Disappointingly, transfer hydrogenation of **6a** in the presence of Noyori-type catalysts (Scheme 3, Method C) failed and mostly the starting material was recovered. The isolated product had poor enantiopurity. The best results were achieved when enone **6a** was subjected to (*S*)-*t*-Bu-Pmrox/Ni-mediated 1,2-reduction with pinBH under conditions reported by Chen and co-workers.[39] Under conditions presented in Scheme 3 (method D), the desired alcohol **3a** was obtained in 90% yield (over 95% conversion of starting material) and in very high enantioselectivity (94% ee).

The reduction proceeded efficiently also for other simple β,β-disubstituted enones bearing *n*-butyl (**3a**), *n*-hexyl (**3b**), i-butyl (**3c**), and benzyl (**3d**) substituents (Scheme 4). Reduction of enones bearing hindered alkyl groups such as i-propyl or cyclohexyl ones, proceeded still efficiently, though the reaction time had to be extended up to 48 h. In addition, their reduction provided the corresponding allyl alcohols **3e** and **3f** with slight lower enantiopurity (Scheme 4). The replacement of R^1 = Me group in **3a** by *n*-hexyl, as in **3g**, caused the same effect. Also, in this case, extension of reaction time to

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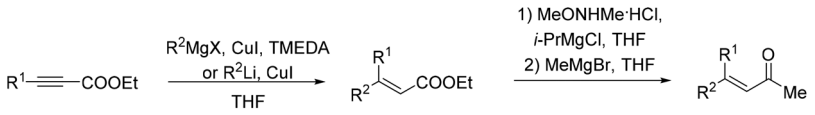
Table 1 Synthesis of α,β-unsaturated esters **5** and enones **6**

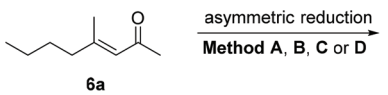


4a, R^1: Me
4b, R^1: *n*-hexyl (hex)
4c, R^1: cyclohexyl (Cy)

5 **6**

R^1	R^2	Yield of **5** [%]	*E* : Z ratio[a]	Yield of **6** [%]
Me	Bu	90(**5a**)	95>	79(**6a**)
Me	Hex	99(**5b**)	95>	88(**6b**)
Me	i-Bu	96(**5c**)	95>	76(**6c**)
Me	i-Pr	75(**5d**)[b]	95>	66(**6d**)
Me	Cy	85(**5e**)	95>	77(**6e**)
Me	Bn	96(**5f**)	95>	82(**6f**)
Hex	Bu	95(**5g**)	5 : 95	71(**6g**)
Hex	i-Pr	94(**5h**)	95 : 5	87(**6h**)
Cy	i-Pr	89(**5i**)	5 : 95	84(**6i**)

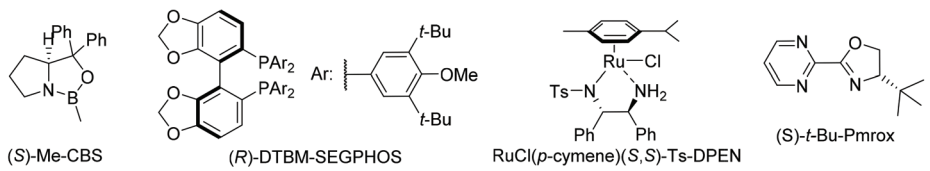
[a] Determined by ^{1}H NMR. [b] Lower yield due to the volatility of the product.



6a **3a**

Method	Yield of **3a** [%]	*ee* [%] (*enantiomer*)
A	87	−79 (*R*)
B	91	+75 (*S*)
C	15	+31 (*S*)
D	**90**	**+94 (*S*)**

Method A: (S)-(-)-2-Methyl-CBS-oxazaborolidine (25 mol%), $BH_3 \cdot SMe_2$
Method B: $Cu(OAc)_2$ (3 mol%), (*R*)-DTBM-SEGPHOS (3 mol%), DEMS, Et_2O, −25 °C
Method C: RuCl(*p*-cymene)(*S*,*S*)-Ts-DPEN (10 mol%), HCOOH:Et_3N 5:2, rt
Method D: $Ni(COD)_2$ (2 mol%), (*S*)-^{t}Bu-Pmrox (2.4 mol %), DABCO, pinBH, toluene, −25 °C



(*S*)-Me-CBS (*R*)-DTBM-SEGPHOS RuCl(*p*-cymene)(*S*,*S*)-Ts-DPEN (S)-*t*-Bu-Pmrox

Scheme 3

48 h was required. The introduction of a bulky group as R^1 strongly affected the reduction process. In the case of the synthesis of alcohols **3h** and **3i**, even a 3-fold increase of reaction time did not result in complete conversion of the starting material. Moreover, in both cases, a significant decrease of enantioselectivity was observed. Further attempts at re-optimization of the reaction did not accelerate the reaction.

The observed difficulties in the synthesis of enantiopure alcohols **3h** and **3i** encouraged us to attempt to prepare them *via* kinetic resolution of racemates. Initially, the effectiveness of this approach was tested for model alcohol ***rac*-3a** (Scheme 5). Its treatment with vinyl acetate in the presence of lipase B from *Candida Antarctica* provided, after 16 h, the corresponding (*S*)-allyl alcohol **(*S*)-3a** in 47% yield and with high 89% ee enantiopurity. The accompanying (*R*)-acetate **7** was isolated in 47% yield and its enantiopurity was 91% ee. Kinetic resolution of ***rac*-3h** and ***rac*-3i** required dramatic increase in reaction time to 11 days, for the former, and to 40 days(!) for the latter. These two examples clearly show how challenging the synthesis of enantiopure type **3h**/**3i** allyl alcohols bearing sterically hindered substituents is.

Recently, we have demonstrated that a sequential functionalization of propargyl alcohols is an efficient method for the preparation of complex allyl alcohols.[36,37,44] Therefore, we decided to check whether the developed protocols will be suitable for the current studies. Initially, easily available (*S*)-hept-1-yn-3-ol (**10**) was transformed to β-vinylstannane **11** following our previous protocol (Scheme 6).[36] After Sn-halogen

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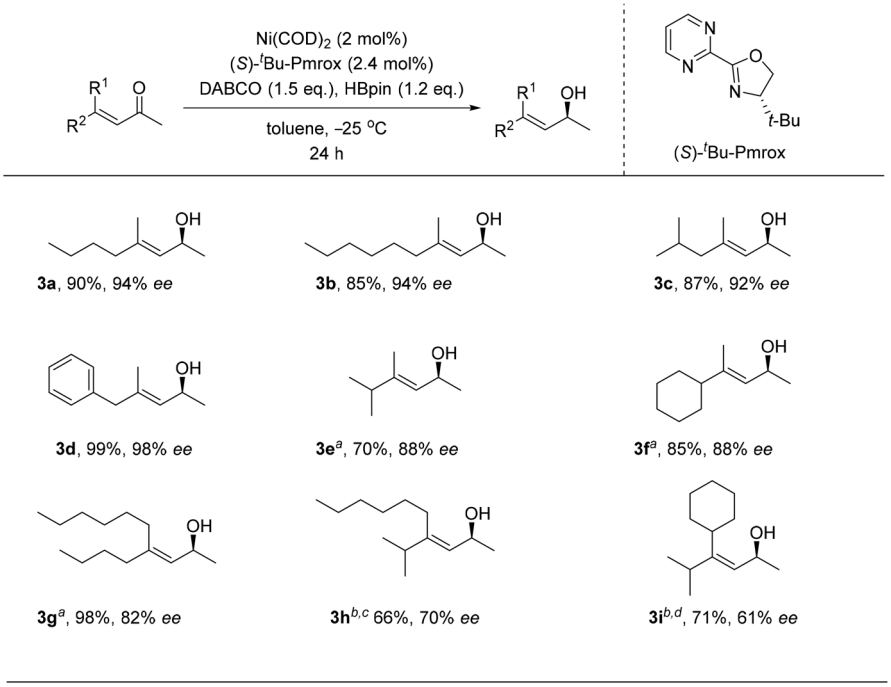
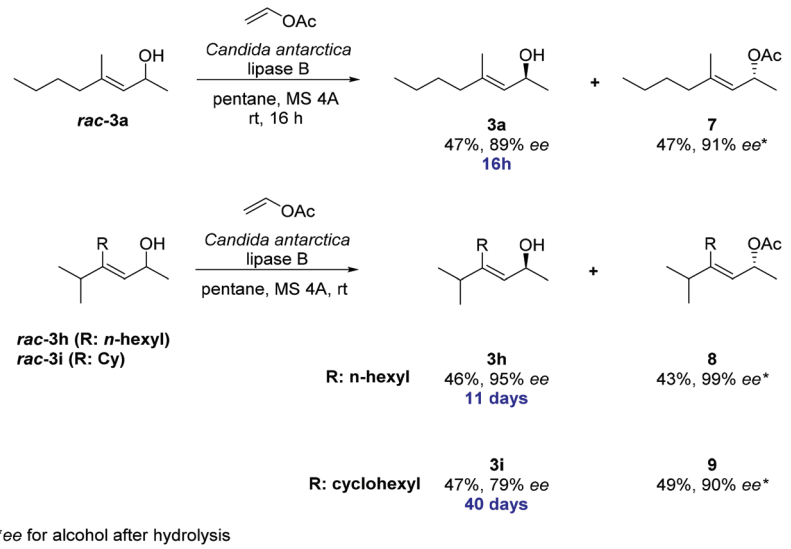


[a] 48 h;
[b] Ni(COD)2 (4 mol%), (S)-tBu-Pmrox (4.8 mol%), DABCO (3.0 eq.), HBpin (2.4 eq.)
[c] 75% conversion after 72 h
[d] 48 h at -25 °C, then 24 h at rt; 82% conversion after 72 h

Scheme 4



*ee for alcohol after hydrolysis

Scheme 5

exchange, the resulting vinyl iodide **12** was subjected to the Negishi cross-coupling reaction. The cross-coupling with simple alkyl organozinc reagents proceeded smoothly (in *ca.* 3–4 h), with complete conversion of the starting material, and without the formation of a protodehalogenation side product when $Pd(dppf)Cl_2$ was used as the catalyst.[45] Disappointingly, this process was limited to the introduction of simple linear alkyl groups such as methyl, ethyl or *n*-butyl. In the case of alcohols bearing a secondary alkyl group (*e.g.* i-Pr or Cy, Scheme 6), the corresponding vinylstannanes were formed non-selectively to provide difficult to separate mixtures of α and β isomers.

In the next step, β,β-dialkyl substituted allyl alcohols **3** were transformed into *tert*-allylamines through the [3,3]-sigmatropic

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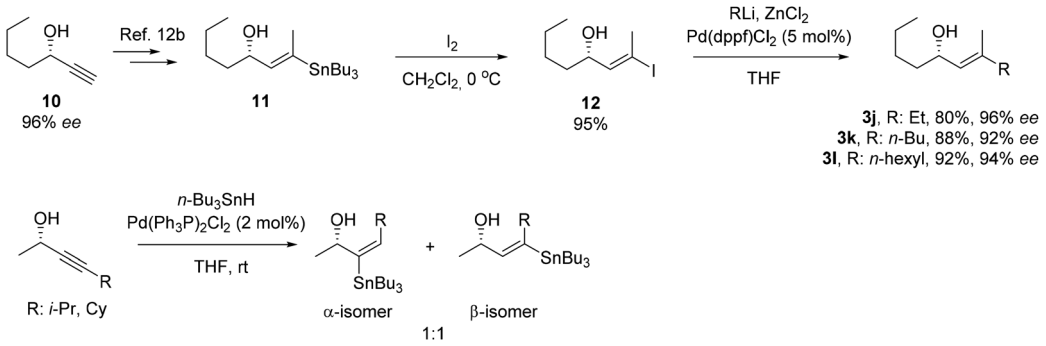
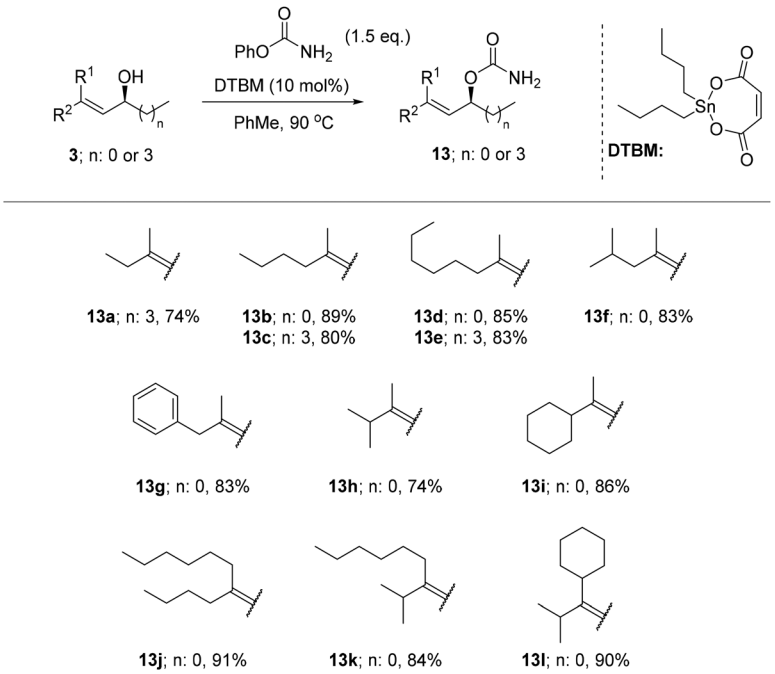


Scheme 6



Scheme 7

Ichikawa rearrangement reaction.[46,47] First, they were carbamoylated by the treatment with phenyl carbamate in the presence of dibutyltin maleate (DBTM) as a catalyst (Scheme 7).[48,49] The resulting carbamates **13** were treated with TFAA (2 equiv.) in the presence of Et_3N (6 equiv.). After 30 min, *t*-BuOLi was added to provide *N*-Boc protected allylamines **14** with high overall yields after 3 steps. The rearrangement proceeded efficiently for a wide range of alkyl substituents regardless of whether they were simple linear groups or sterically hindered substituents. Importantly, the rearrangement proceeded stereoselectively with complete chirality transfer and generated the new tetrasubstituted carbon stereocenter enantiospecifically (Scheme 8).

The transformations presented above, leading to α,α-dialkyl substituted allylamines, proceeded smoothly not only on a small scale (<1 mmol) but are easily scalable. This was exemplified by a gram-scale synthesis of allylamine **14b** (Scheme 9). To maximize the efficiency of the process and minimize any loss of intermediates, the individual steps were combined in three blocks, and intermediate isolation/purification was mostly limited to a simple extraction. Thus, 20 mmol (2.24 g) of alkyne **4a** was transformed into Weinreb amide **15**. Next, it was subjected to Grignard reagent addition and, after simple extraction, to the enantioselective reduction. The crude alcohol was transcarbamoylated to provide product **13b**. Finally, the carbamate was rearranged to amine **14b**. As a result, the presented formal 7-step synthesis required only three chromatographic purification operations: (1) amide **15** (to eliminate slight contamination with the *Z* isomer), (2) carbamate **13b** (slight impurities can affect the efficiency of the rearrangement), and (3) final amine **14b**. The remaining steps required only simple extraction. The Ichikawa transformation was also efficient on a larger scale, although, in order to facilitate the process, the reaction temperature was decreased to

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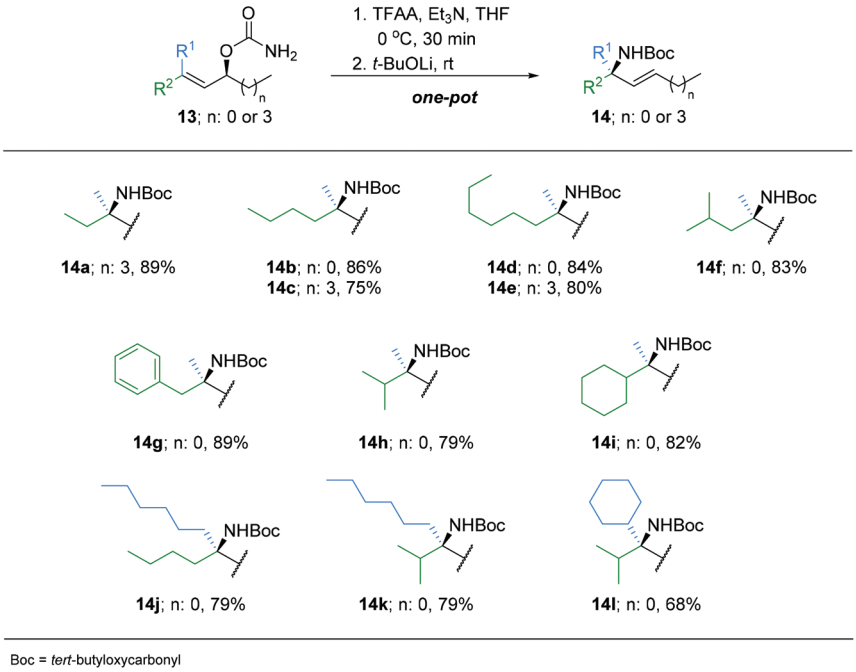
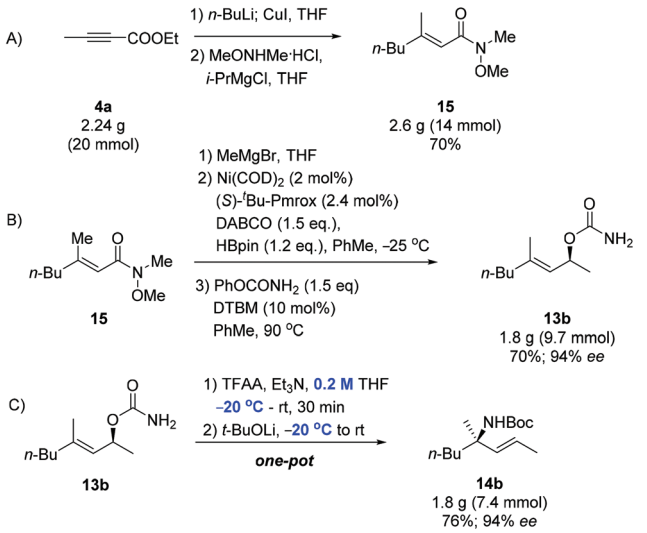


Scheme 8



Scheme 9

–20 °C (to avoid overheating of the reaction mixture during the addition of a larger amount of TFAA). Moreover, in case of the gram-scale synthesis, reaction concentration could be increased from 0.05 M (for <1 mmol scale) to 0.2 M, which allowed to reduce the amount of solvent and, as a result, the amount of waste. Thus, starting from 20 mmol (2.24 g) of alkyne **4a**, 1.8 g (7.4 mmol) of product **14b** was obtained with overall yield 37% (Scheme 9).

It should be stressed that the reported strategy, based on sigmatropic rearrangement of allyl carbamates **13**, allows for the preparation of vast classes of *N*-functionalized allylamine derivatives. As we already demonstrated in the past,[36] a simple replacement of *t*-BuOLi by other nucleophilic agents, including alkoxides (or alcohols), *C*-nucleophiles (organometallics, enolates), *N*-nucleophiles (amines, hydrazines, oximes *etc.*), *H*-nucleophiles, enables direct access to carbamates, amides, and urea derivatives.

Finally, the resulting allylamines **14** were ozonolyzed, followed by $NaBH_4$ reduction to provide *N*-Boc protected enantiopure vicinal amino alcohols **16** (Scheme 10) in very good yield after 2 steps. In addition, type **16** amino alcohols can be easily transformed into their *N*-Ts congeners **17** by treatment of **16** with 4 M HCl in dioxane followed by tosylation of the crude amine with *p*-TsCl in the presence of Et_3N, as demonstrated in Scheme 10. For more hindered amino alcohols **16i,j**, the tosylation under standard conditions was less effective. However, the replacement of the base with TMEDA and the solvent with MeCN enhanced the process. Both types of these β-amino alcohols were proved to be highly valuable building blocks in target-oriented synthesis as well as valuable organocatalysts, chiral auxiliaries, and chiral templates.[5,50–52]

Nitrogen-containing heterocycles with a morpholine,[53–59] piperazine[56–61] or aziridine[62,63] ring are important pharmacophores in medicinal chemistry. Although vast number of synthetic protocols for the preparation of the mentioned heterocyclic scaffolds are known, less attention has been devoted to develop approaches for *C*-substituted analogues, particularly those bearing tetrasubstituted carbon stereocenters, due to limited access to suitable starting materials or efficient, highly stereoselective synthetic protocols. From this point of view, the reported protocol for the preparation of enantiopure β-*tert*-amino alcohols should be highly attractive as a tool for syn-

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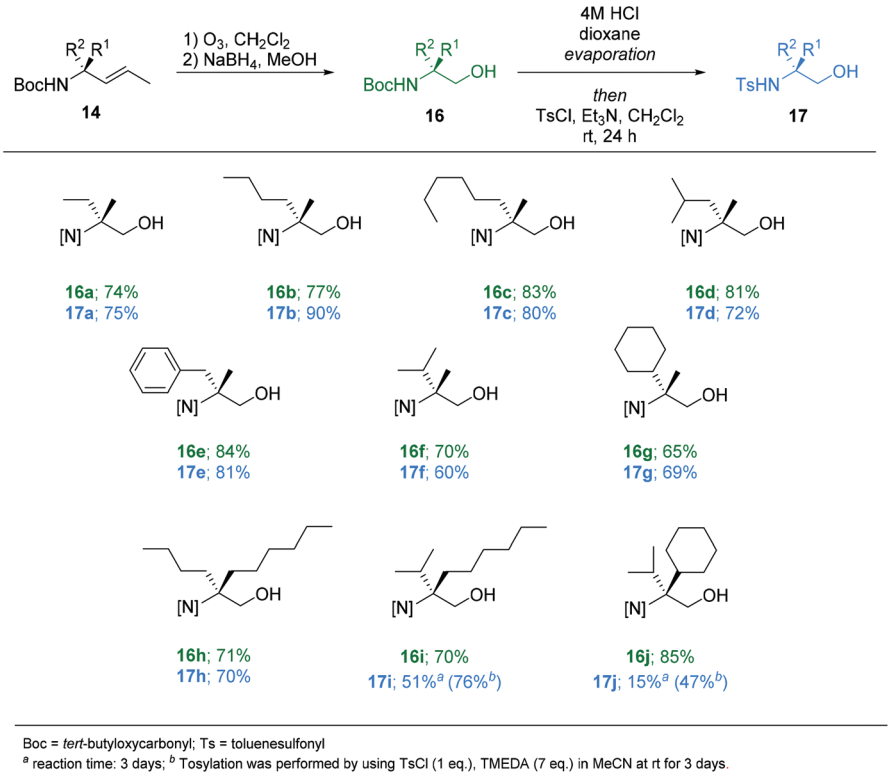


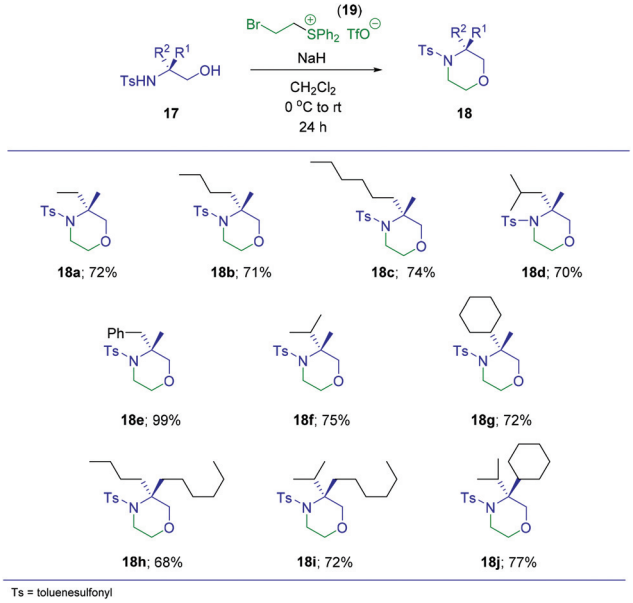
Boc = *tert*-butyloxycarbonyl; Ts = toluenesulfonyl
[a] reaction time: 3 days; [b] Tosylation was performed by using TsCl (1 eq.), TMEDA (7 eq.) in MeCN at rt for 3 days.

Scheme 10

thetic and medicinal chemists. Thus, to demonstrate the utility of the reported strategy for the preparation of enantiopure β-*tert*-amino alcohols, their conversion into the mentioned heterocyclic scaffolds was performed.

As already mentioned, the morpholine scaffold has been classified as a privileged structural motif in drug discovery and continues to have increasing presence in lifesaving medications.[53–59] Morpholines are also valuable building blocks. Therefore, we decided to transform amino alcohols **16** or **17** into enantiopure *gem*-disubstituted heterocycles **18**. An intuitive approach based on the cyclization of **16**/**17** with a dielectrophilic synthon such as dihalide is rather less efficient and often provides side elimination products. For this reason, we turned our attention to more efficient annulation agents such as bromoethylsulfonium salts reported by Aggarwal and co-workers.[64] In the presence of salt **19** and NaH as a base, compounds **17** were easily cyclized to non-racemic morpholines **18** in very good yields (Scheme 11).

Next, the conversion of 1,2-amino alcohols **17** into the corresponding aziridines **20** was performed. Two synthetic protocols were tested. In the first approach, amino alcohol **17b** was treated with MsCl in the presence of Et_3N. In the second approach, the cyclization was performed under Mitsunobu reaction conditions. The latter reaction provided the desired product in higher yield, thus these conditions were applied for other amino alcohols **17**. In all cases, the desired enantiopure aziridines **20** were obtained in excellent yields (Scheme 12).



Ts = toluenesulfonyl

Scheme 11

The final demonstration of the utility of amino alcohols **16**/**17** in the synthesis of medicinally important heterocycles was the transformation of selected compounds **17** into the corresponding piperazine systems, which, as already mentioned, are important systems for organic and medicinal chemistry.[56–61] Thus, azridines **20** were subjected to ring-opening with $TsNH_2$

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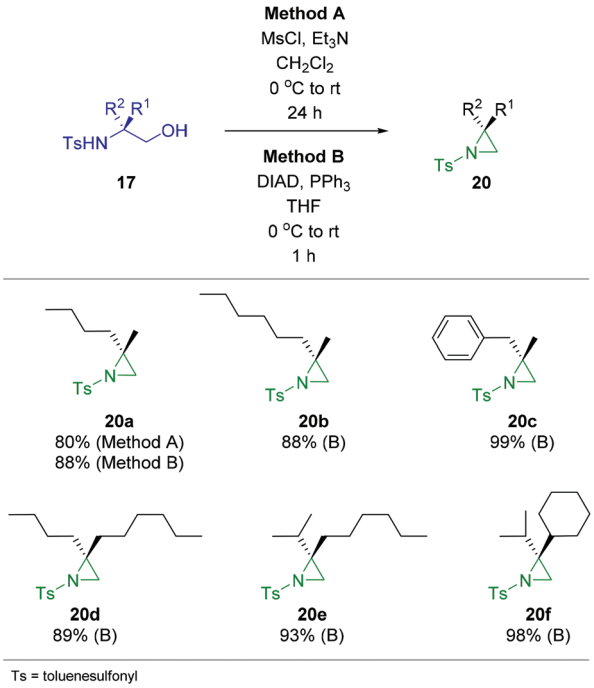
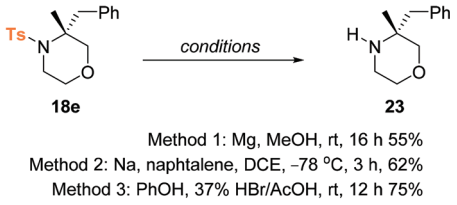


Scheme 12



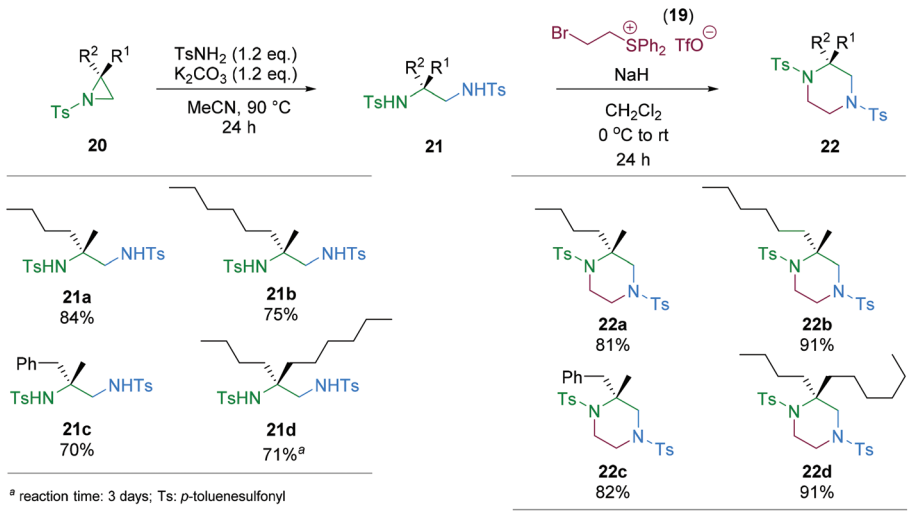
Scheme 14

to furnish diamine derivatives **21** (Scheme 13). Next, in the presence of sulfonium salt **19** and base, diamines **21** underwent a cyclization process to provide enantiopure piperazines **22** bearing a tetrasubstituted carbon stereocenter in high yields.

The Ts group from the obtained heterocycles can be removed to provide *N*-free compounds following literature protocols (Scheme 14).[65,66] For instance, the *N*-deprotection of **18e** by the treatment with Mg in dry MeOH at rt provided desired morpholine **23** in 55%. In the presence of Na/naphthalene in DME at −78 °C product **23** was obtained in 62% yield. The best yield (75%) was obtained when morpholine **18e** was treated with 3-fold excess of PhOH in 37% HBr in AcOH.

Conclusions

In summary, a method for the preparation of enantiopure β-*tert*-amino alcohols bearing a tetrasubstituted *C*-stereocenter was reported. These compounds were obtained through enantiospecific sigmatropic rearrangement of allyl carbamates as a key step. The latter were prepared from the corresponding β,β-dialkyl substituted non-racemic allyl alcohols. In addition, the asymmetric synthesis of such highly substituted allylic alcohols *via* either enantioselective 1,2-reduction of enones, enzymatic kinetic resolution, or functionalization of chiral propargyl alcohols, with a discussion of the scope and limitations of each method, was reported. The mentioned rearrangement step proceeded efficiently to provide the desired products (allylamines) in high yields and with complete chirality transfer; these were next easily transformed into target enantiopure β-*tert*-amino alcohols. It is worth to highlight that the reported method allowed for the preparation of complex non-racemic α-*tert*-allylamines and, in turn, β-*tert*-amino alcohols (bearing tetrasubstituted *C*-stereocenter) either on a small (<1 mmol) or on a gram scale (>7 mmol), starting from simple, commercially available alkynes. Finally, the importance of the developed method was demonstrated by the synthesis of selected hetero-



Scheme 13

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cyclic scaffolds (morpholines, aziridines, and piperazines) starting from the synthesized β-*tert*-amino alcohols.

Conflicts of interest

There are no conflicts to declare.

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