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RESEARCH ARTICLE

O2-Assisted Four-component Reaction of Vinyl Magnesium Bromide with Chiral *N-tert*-Butanesulfinyl Imines To Form *syn*-1, 3-Amino Alcohols**

Runping Wang,† Jingfan Luo,† Chunmei Zheng, Hongyun Zhang, Lu Gao and Zhenlei Song*

R. P. Wang,† J. F. Luo,† C. M. Zheng, H. Y. Zhang, Prof. Dr. L. Gao, Prof. Dr. Z. L. Song
Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry and Sichuan Province, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu, 610041, China
E-mail: zhenleisong@scu.edu.cn

†These two authors contributed equally to this work.
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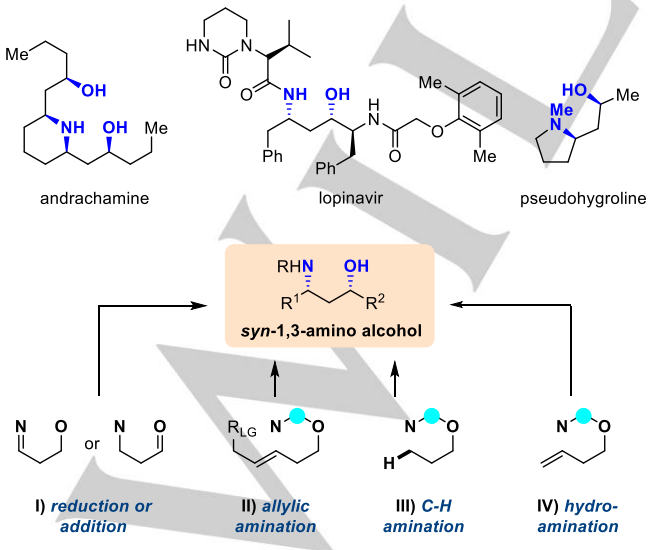
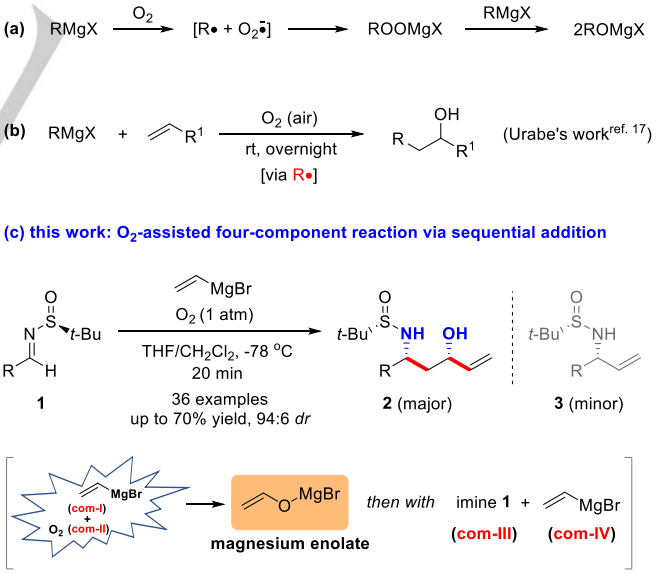
Abstract: An O_2-assisted, four-component reaction has been developed to synthesize a wide range of *syn*-1,3-amino alcohols in one step. The reaction proceeds by oxygenation of vinyl magnesium bromide (*component-I*) with O_2 (*component-II*) to give a magnesium enolate of acetaldehyde, which undergoes addition to a chiral *N-tert*-butanesulfinyl imine (*component-III*) followed by a sequential addition with excess vinyl magnesium bromide (*component-IV*). The approach allows diastereoselective synthesis of *anti*/*syn*- and *syn*/*syn*-3-amino-1,5-diols in good yields with high diastereoselectivity. The method was illustrated in an efficient, four-step synthesis of piperidine alkaloid (-)-2'-*epi*-ethylnorlobelol.

Introduction

1,3-Amino alcohols are important motifs in many pharmaceuticals and natural products (Scheme 1, upper) either within an open chain (e.g. lopinavir[1]) or embedded in a ring structure (e.g. andrachamine and pseudohygroline[2]). Additionally, 1,3-amino alcohols are useful chiral building blocks in asymmetric synthesis functioning as chiral ligands and auxiliaries.[3] In this context, developing efficient approaches towards 1,3-amino alcohols in a diastereo- and enantioselective manner has remained an active and important research area in organic synthesis. Diastereoselective access to 1,3-amino alcohols typically involve reduction of 1,3-amino ketones,[4] 1,3-hydroxy imines[5] or 2,3-dihydroisoxazoles,[6] or the addition of organometallic reagents to 1,3-amino aldehydes and ketones (Scheme 1-I).[7] Palladium-catalyzed intramolecular allylic amination of *N*-tosyl carbamate,[8] hemiaminal[9] or trichloroacetimidates [10] derived from 2-pentene-1,5-diol enables a cyclization strategy for the synthesis of 1,3-amino alcohol variants (Scheme 1-II). Recent elegant progresses in transition-metal-catalyzed aliphatic C−H amination[11] with nitrenes,[12] allylic C−H amination (Scheme 1-III)[13] and hydroamination of homoallenyl carbamate (Scheme 1-IV)[14] are emerging as straightforward and atom-economical route to this motif.



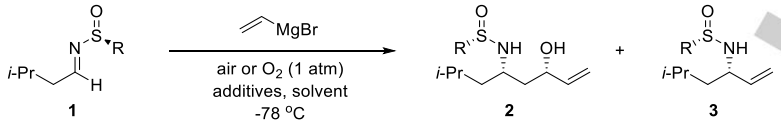
Scheme 1. Representative bioactive molecules and natural products containing *syn*-1,3-amino alcohol, and general strategies towards this motif.



Scheme 2. (a) General profile of oxygenation of Grignard reagents. (b) Urabe's work: air-assisted addition of Grignard reagents to olefins. (c) This work: O_2-assisted four-component reaction of vinyl magnesium bromide and (*S*)-*N-tert*-butanesulfinyl imines **1** to form *syn*-1, 3-amino alcohols **2**.

Grignard reagents (RMgX) are well-known to oxygenate with O_2 to give the corresponding magnesium alkoxide (ROMgX) (Scheme 2a).[15] The reaction is proposed to proceed via a radical

Table 1. Screening of Reaction Conditions[a]



Entry	$CH_2CHMgBr$ (equiv.)	R	Air or O_2	t^1 [b]	t^2 [b]	Additives (1.1 equiv.)	Solvent /mL (I+II) [c]	Yield (**2**) [d]	*dr* (**2**) [e]	Yield (**3**) [e]
1	3.0	*t*-Bu (**1a**)	/	/	3 h	/	THF/4.5 (1.5+3)	5%	75:25	79%
2	5.0	*t*-Bu (**1a**)	air	12 h	12 h	/	THF/5.5 (2.5+3)	17%	75:25	22%
3	6.0	*t*-Bu (**1a**)	air	12 h	12 h	/	THF/6 (3+3)	35%	75:25	44%
4	6.0	*t*-Bu (**1a**)	O_2	3 min	1 h	/	THF/6 (3+3)	45%	75:25	45%
5	6.0	*t*-Bu (**1a**)	O_2	5 min	1 h	/	THF/6 (3+3)	52%	75:25	40%
6	6.0	*t*-Bu (**1a**)	O_2	10 min	1 h	/	THF/6 (3+3)	30%	75:25	51%
7	6.0	*t*-Bu (**1a**)	O_2	5 min	1 h	$AlMe_3$	THF/6 (3+3)	N.R.	/	N.R.
8	6.0	*t*-Bu (**1a**)	O_2	5 min	1 h	$ZnMe_2$	THF/6 (3+3)	53%	75:25	34%
9	6.0	*t*-Bu (**1a**)	O_2	5 min	1 h	$ZnCl_2$	THF/6 (3+3)	N.R.	/	N.R.
10	6.0	*t*-Bu (**1a**)	O_2	5 min	15 min	/	THF/CH_2Cl_2/6 (3+3)	55%	90:10	32%
11	6.0	*t*-Bu (**1a**)	O_2	5 min	15 min	/	THF/CH_2Cl_2/7 (3+4)	62%	90:10	35%
12	6.0	4-MeC_6H_4 (**1b**)	O_2	5 min	15 min	/	THF/CH_2Cl_2/7 (3+4)	32%	≥95:5	/

[a] Reaction conditions: **1** (0.5 mmol), vinyl magnesium (1.0 M in THF) at -78 ºC. [b] t^1: passing air or O_2 (1 atm) through the solution; t^2: addition with imine **1**. [c] solvent I: THF to dissolve vinyl magnesium; solvent II: THF or CH_2Cl_2 to dissolve imine **1**. [d] Isolated yields. [e] The ratios were determined by ^{1}H NMR of crude products.

mechanism to yield a peroxide species (ROOMgX). Then reduction of the peroxide with RMgX generates ROMgX.[16] The overall yield of this reaction is good in the case of alkyl Grignard reagents, but poor in the case of aryl ones. Although this chemistry was discovered almost 120 years ago, its synthetic utility has barely been explored, with exception of work by Urabe and co-workers in 2005 (Scheme 2b).[17] They took advantage of the radical species (R•) generated by oxidation of Grignard reagents in air to develop a one-pot, three-component coupling of Grignard reagent, olefin, and O_2, which directly afforded alcohols.

Here we report another synthetically valuable utility of Grignard reagent oxygenation in a four-component coupling process (Scheme 2c). Oxygenation of vinyl magnesium bromide (*component-I*) with O_2 (*component-II*) gives the corresponding magnesium enolate intermediate (CH_2=CHOMgX), which undergoes addition to chiral *N-tert*-butanesulfinyl imine **1**[18] (*component-III*) followed by addition with excess vinyl magnesium bromide (*component-IV*). The reaction enables an efficient one-step approach to diverse *syn*-1,3-amino alcohols **2** predominantly, while normal addition to give allylic sulfonamide **3** proceeds as a minor pathway. Our approach showcases a strategically distinct method toward *syn*-1,3-amino alcohols in constrat to those shown in Scheme 1, and has substantial utility in organic synthesis.

Results and Discussion

Optimization of Reaction Conditions. (*S*)-*N-tert*-butanesulfinyl imines **1** were synthesized by the procedure developed by Ellman and co-workers in 1999.[18a] In the presence of Ti(O*i*-Pr)$_4$ (2.8 equiv.) as the Lewis acidic dehydrating agent, direct condensation of (*S*)-*N-tert*-butylsulfenamide (1.1 equiv.) with aldehydes (1.0 equiv.) in anhydrous CH_2Cl_2 at room temperature affords a variety of (*S*)-*N-tert*-butanesulfinyl imines **1** in good yields with complete *E*-selectivity (see Supplementary Information on pages S3-S23 for details). Our studies began after we observed that during the addition of vinyl magnesiumbromide to (*S*)-*N-tert*-butanesulfinyl imine **1a** in THF at -78 ºC under argon, the normal addition product allylic sulfinamide **3a** was obtained in 79% yield, while the synthetically more valuable *syn*-1,3-amino alcohol **2a** was also obtained in 5% yield with 75:25 *dr* (Table 1, entry 1). The origin of **2a** was unclear, but its secondary hydroxyl group led us to speculate that oxygen was involved. Thus, we repeated the reaction in dry air to favor the formation of **2a**. As expected, the yield of **2a** increased to 17% after 12 h of reaction (entry 2). Increasing the loading of vinyl magnesium bromide to 6.0 equiv. gave **2a** in a higher yield of 35% (entry 3), along with 44% of **3a**. An even higher yield of **2a** was obtained by passing pure oxygen gas through the solution of vinyl magnesium bromide in THF, and then removing the oxygen balloon before the addition of **1a**. The duration of the sparging proved important: sparging with oxygen for 5 min gave higher yield (52%, entry 5) than sparging for shorter or longer (entries 4 and 6). Of various Lewis acids as additives, only $ZnMe_2$ provided comparable yield of 53% (entry 8), while other Lewis acids completely inhibited formation of **2a** and **3a** (entries 7 and 9). Using the mixed solvent system containing THF and non-coordinating solvent CH_2Cl_2 significantly improved diastereoselectivity (entry 10), leading to **2a** in an optimal yield of 62% with a *syn*/*anti* ratio of 90:10 (entry 11). Reaction of (*S*)-*N-p*-toluenesulfinyl imine **1b**[19] gave the corresponding *syn*-1,3-amino alcohol **2b** with complete *syn*-selectivity but only 32% yield (entry 12), indicating lower overall efficiency than with (*S*)-*N-tert*-butanesulfinyl imine **1a**.

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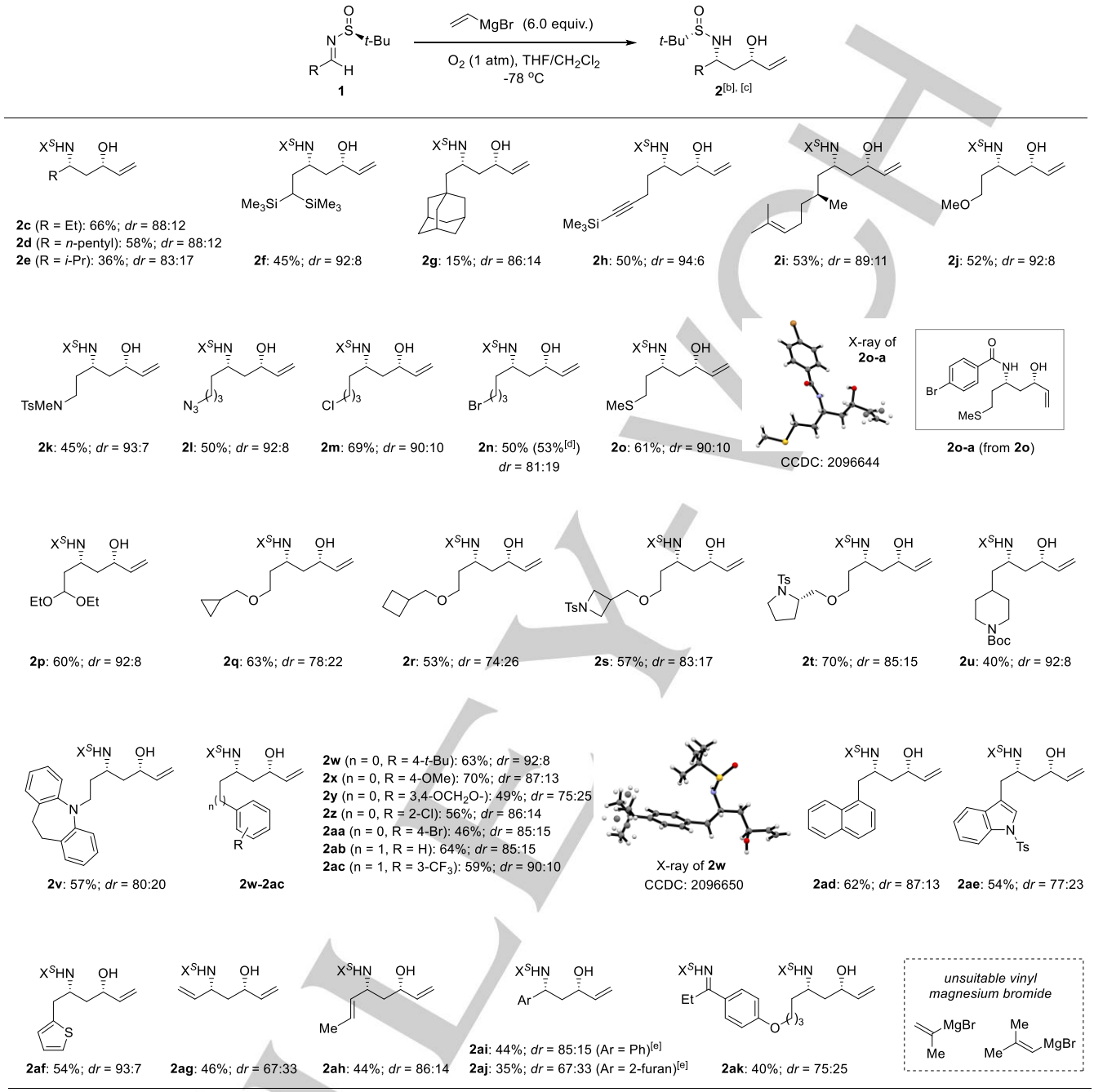
Table 2. Scope of (*S*)-*N*-*tert*-butanesulfinyl Imines **1** and Vinyl Magnesium Bromides[a]



[a] Reaction conditions: O_2 (1 atm in balloon) and vinyl magnesium (3.0 mmol, 1.0 M in THF), 5 min, -78 ºC; then addition of imine 1 (0.5 mmol) in CH_2Cl_2 (4 mL), 15 min, -78 ºC. [b] Isolated yields. [c] The ratios were determined by ^{1}H NMR of crude products. [d] Scaled-up to 4 mmol of imine. [e] sparging O_2 for 5.5 min, and vinyl magnesium bromide (5.0 equiv.).

Scope of Imines. The scope of (*S*)-*N*-*tert*-butanesulfinyl imine **1** was examined using vinyl magnesium bromide (Table 2). The yield differences among the ethyl group-substituted **2c**, **2f** containing a geminal bis(silyl)group[20] and **2g** bearing a much bulkier adamantyl group indicated a steric bias that bulkier substituents on the imine reduced the yield. The reaction tolerated a silyl alkynyl group (**2h**), which could be converted into other functionalities via a variety of transformations, such as Hiyama-Denmark cross-coupling.[21] Imines containing various heteroatom-functionalities such as ether, sulfonamide, azide,halogen, sulfide or acetal served as good substrates, giving **2j-2p** in good yields with generally high diastereoselectivities. No oxidation of the sulfide group was observed in the formation of **2o**. The reaction proved suitable for a large-scale synthesis of **2n** using 4 mmol of imine, which provided a comparable yield of 53%. Good applicability was also

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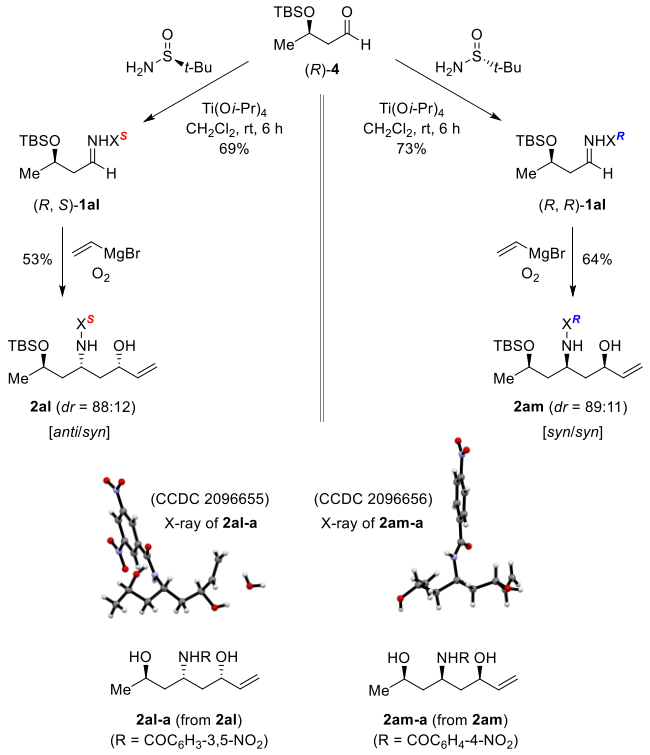
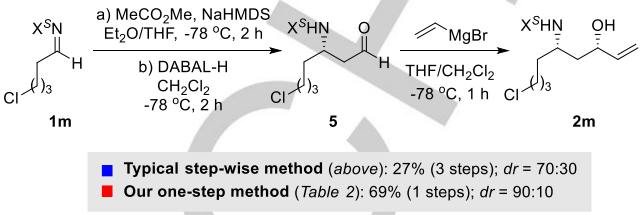


Scheme 3. Synthesis of *anti*/*syn*-3-amino-1,5-diol **2al** and *syn*/*syn*-3-amino-1,5-diol **2am**.

observed for imines containing cyclopropane, cyclobutane, or *N*-heterocycles with 4-7 members (**2q**-**2v**). The reaction functioned well with a wide range of alkyl imines bearing a phenyl ring substituted with electron-donating or -withdrawing groups, or alkyl imines bearing a heterocyclic group such as 2-thiophene or 3-indole at the terminal position of the alkyl chain (**2w-2af**). Suitable substrates also included α,β-unsaturated imines, which gave **2ag** and **2ah**, useful precursors to form cyclic 1,3-amino alcohols via the ring closing metathesis (RCM) reaction.[22]

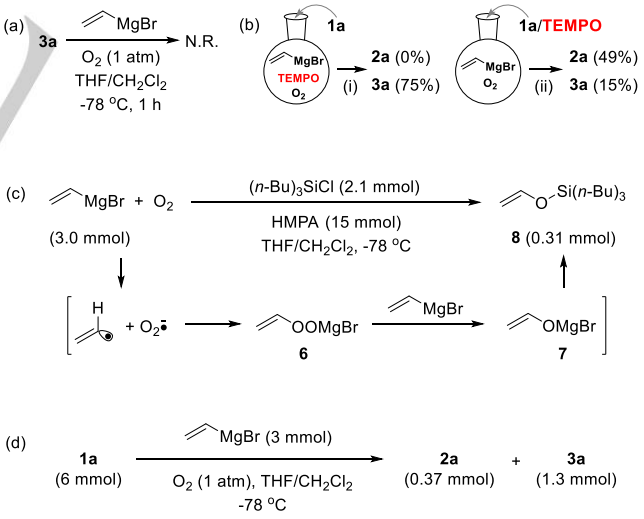
In contrast to alkyl imines, aryl imines were much more challenging substrates for this transformation. The reaction gave allylic sulfinamide **3** as the predominant product via the normal addition, while the desired *syn*-1,3-amino alcohols were obtained in only moderate or poor yields (e.g. **2ai, 2aj)**. Ketimine was less reactive than aldimine, failing to undergo either normal or sequential addition. We exploited the reactivity difference between ketimine and aldimine to synthesize **2ak** in 40% yield: the aldimine reacted selectively, while the ketimine remained untouched. The reaction appears suitable only for unsubstituted vinyl magnesium bromide: reaction with either 1-methyl- or 3,3-dimethyl vinyl magnesium bromide gave complex mixtures lacking the desired 1,3-amino alcohol products.

Synthesis of 3-Amino-1,5-diol. To demonstrate the synthetic utility of this sequential addition, we applied it to synthesis of 3-amino-1,5-diol synthons (Scheme 3). Condensation of TBS-protected 3-hydroxyl aldehyde (*R*)-**4** with (*S*)-or (*R*)-*N*-*tert*-butylsulfenamide gave rise to the respective diastereomers (*R*, *S*)-**1al** and (*R*, *R*)-**1al**. Both served as good substrates under the optimal reaction conditions to undergo predominantly *syn*-addition (*dr* = 90:10), leading to *anti*/*syn*-isomer **2al** in 53% yield from (*R*, *S*)-**1al**, and to *syn*/*syn*-isomer **2am** in 64% yield from (*R*, *R*)-**1al**. The predominant *syn*-addition in both cases indicated that the *tert*-butanesulfinyl moiety controlled the stereochemical outcome, with minimal influence from the β-stereogenic center in the imine.



Scheme 4. Comparison of the synthesis of **2m** via the step-wise method and our method.

Comparison of Traditional Step-wise Method and Our Method. Our approach was more efficient at synthesizing *syn*-1,3-amino alcohols **2** (e.g. **2m**) than the typical step-wise process shown in Scheme 4, which requires three steps: (1) Mannich-type addition of the sodium enolate of methyl acetate to imine **1m**, (2) reduction of the ester group with DIBAL-H, and (3) addition of vinyl magnesium bromide to the resulting 1,3-amino aldehyde **5**. While this three-step process provided 1,3-amino alcohol **2m** with the desired *syn*-stereocontrol, the overall yield was only 27% and *dr* was poor at 70:30. Our method, in contrast, required only one step and led to **2m** in much higher yield of 69% and better *dr* of 90:10 (Table 2).



Scheme 5. Mechanistic studies.

Mechanistic Studies. In mechanistic studies, we ruled out the possibility that *syn*-1,3-amino alcohol **2a** formed from the normal addition product **3a** (Scheme 5a). We also clarified the likely role of radicals in the reaction by conducting two experiments with the radical trapping reagent TEMPO. Sparging O_2 gas into a solution of vinyl magnesium bromide and 3.0 equiv. of TEMPO in THF, then adding imine **1a** gave the normal adduct **3a** in 75% yield without any 1,3-amino alcohol **2a** (Scheme 5b-i). In the second

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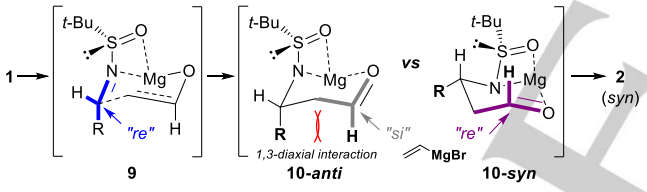
experiment, adding the solution of imine **1a** and TEMPO in CH_2Cl_2 to O_2-saturated vinyl magnesium bromide gave **2a** in 49% yield, with 15% yield of **3a** (Scheme 5b-ii). The results from these two experiments suggest that the radical process participates in the reaction of vinyl magnesium bromide with O_2, but not in the addition to imine.

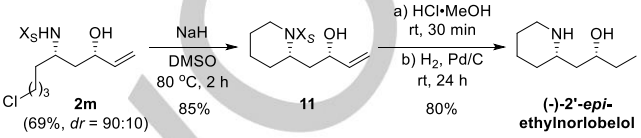
Based on these observations and the well-known fact that alkyl or phenyl Grignard reagents (RMgX) can react with O_2 via a radical pathway to give the corresponding alcohols,[15] we proposed that our reaction might involve a similar oxidation of vinyl magnesium bromide, leading to a magnesium enolate intermediate (Scheme 5c). One-electron transfer from the Grignard reagent to oxygen generates a vinyl radical and anionic oxygen radical. Peroxide **6**[23] then forms through either a radical chain or a non-radical chain process. Vinyl magnesium bromide reduces the peroxide, leading to a magnesium enolate **7**. Formation of **7** was supported by a trapping experiment using $(n\text{-Bu})_3SiCl$, which afforded the corresponding silyl enol ether **8**. This mechanism explains why the duration of O_2-sparging influences efficiency: times shorter than 5 min cannot provide sufficient magnesium enolate, while longer times consume more vinyl magnesium bromide. In order to determine the ratio of magnesium enolate to vinyl magnesium bromide, we used an excess of imine **1a** to trap these two magnesium nucleophiles. The reaction gave rise to 0.37 mmol of **2a** and 1.3 mmol of **3a**, indicating a ratio of magnesium enolate to vinyl magnesium bromide of roughly 1:4.6 (Scheme 5d, see Supplementary Information on pages S45-S46 for details).



Scheme 6. Model of sequentail addition of imine 1 with the magnesium enolate of acetaldehyde and vinyl magnesium bromide.

Based on these results, we propose a mechanistic model of sequential addition to form *syn*-1,3-amino alcohol **2** (Scheme 6). Imine **1** undergoes the first addition with the magnesium enolate of acetaldehyde, which appears more reactive than vinyl magnesium bromide. According to Davis[24] and Ellman's model,[25] a Zimmerman-Traxler-type six-membered transition state **9** is suggested to favor approach of the enolate from the *re*-face of imine, that is consistent with the observed stereochemical outcome at the amino moiety in **2**. The resulting 1,3-amino aldehyde intermediate might adopt a six-membered chelated conformation **10-*syn*** predominantly, as **10-*anti*** suffers a 1,3-diaxial interaction between the R and H groups. In this way, **10-*syn*** is quickly trapped by excess vinyl magnesium bromide, leading to attack on the *re*-face of the carbonyl moiety to form *syn*-1,3-amino alcohol **2**. In some cases, a by-product forms from **10** via sequential addition of the enolate and vinyl magnesium bromide, that was observed in only trace amounts.

Application to Synthesis of (-)-2'-*epi*-Ethylnorlobelol. We applied our approach to the rapid synthesis of (-)-2'-*epi*-ethylnorlobelol (Scheme 7).[26] Cyclization of *syn*-1,3-amino alcohol **2m** (Table 2) with NaH via intramolecular *N*-substitution delivered **11** in 85% yield. Removal of the *N*-*tert*-butanesulfinyl auxiliary of **11** under acidic conditions, followed by hydrogenation of the alkene, gave rise to the target (-)-2'-*epi*-ethylnorlobelolin an overall yield of 80%. Because several piperidine alkaloids, such as sedum and related alkaloids,[2] contain *syn*-1,3-amino alcohol fragment, our method should be useful for the synthesis of many compounds.



Scheme 7. Application of sequential addition to the synthesis of (-)-2'-epi-ethylnorlobelol.

Conclusion

In summary, we have developed an O_2-assisted, four-component reaction to synthesize *syn*-1,3-amino alcohols in one step. The reaction proceeds by oxygenation of vinyl magnesium bromide with O_2 to give the magnesium enolate of acetaldehyde, which undergoes addition to the imine followed by a sequential addition with excess vinyl magnesium bromide, leading to 1,3-amino alcohols with predominant *syn*-stereocontrol. The approach tolerates a wide range of functionality, and also allows the diastereoselective synthesis of *anti*/*syn*- and *syn*/*syn*-3-amino-1,5-diols. The reaction efficacy was demonstrated in an efficient synthesis of (-)-2'-*epi*-ethylnorlobelol, suggesting its utility for preparing bioactive molecules bearing a 1,3-amino alcohol motif. This work showcases a new and valuable utility of Grignard reagent oxygenation. We are exploring more synthetic applications of the scenario in organic synthesis.

Acknowledgements

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Keywords: oxygenation • multi-component reaction • 1,3-amino alcohol • *N*-*tert*-butanesulfinyl imines • vinyl magnesium bromide

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[23] Caution: Despite magnesium peroxide was not produced in an isolable amount and was quickly consumed by excessive vinyl magnesium bromide, care must be taken in the formation of peroxides particularly in a large-scale preparation.

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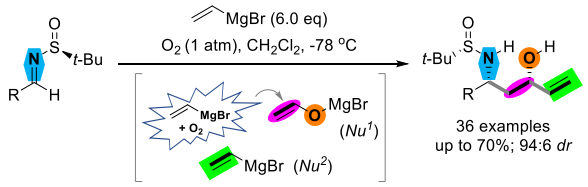
four-component reaction to synthesize syn-1,3-amino alcohol



"***Old reagent with a new use***": Vinyl magnesium bromide, a widely used Grignard reagent, can be oxygenated with O_2 to give a magnesium enolate intermediate. This enables a four-component reaction that efficiently converts chiral *N-tert*-butanesulfinyl imine into a wide range of *syn*-1,3-amino alcohols in one step.