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Asymmetric Aldol−Tishchenko Reaction of Sulfinimines

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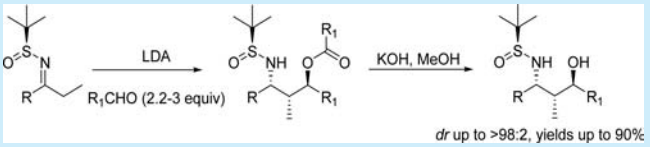
Supporting Information

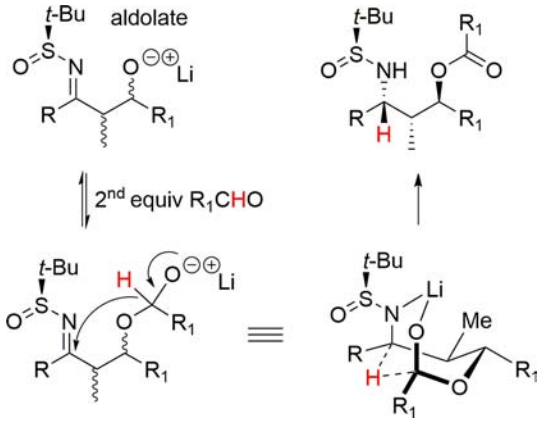
ABSTRACT: Methods for the preparation of 1,3-amino alcohols and their derivatives containing two stereogenic centers usually involve a two-step installation of the chiral centers. An aldol−Tishchenko reaction of chiral sulfinimines which involves the first reported reduction of a C═N in this type of reaction is described. Two and even three chiral centers can be installed in one synthetic step, affording *anti*-1,3-amino alcohols in good diastereo- and enantioselectivity.



1,3-Amino alcohols are useful synthetic intermediates and targets for many natural products and bioactive compounds.[1] For example, marketed drugs such as tramadol, venlafaxine, ritonavir, and lopinavir all contain the 1,3-amino alcohol fragment. Predominantly, 1,3-amino alcohols are synthesized via diastereoselective reduction of enantiomerically pure substrates prepared from Mannich or aldol reactions.[2] More recent examples include an iterative organocatalytic approach[3] and ring opening of chiral piperidines[4] or tetrahydropyrans.[5] Methods which do not rely on additional diastereoselective reduction steps are not widely reported. However, examples do exist, including the synthesis of *syn*-1,3-amino alcohols via Pd-catalyzed allylic amination,[6] the cyclization of trichloroacetimidates,[7] and an indirect route via oxazinanes.[8] Examples for the synthesis of *anti*-1,3-amino alcohols are rare.[9]

We envisaged that an aldol−Tishchenko reaction using an imine derivative could provide these valuable synthons in a diastereoselective manner. Use of a chiral imine derivative could provide enantioselectivity while allowing for the simultaneous introduction of two or more stereogenic centers in a one-step process (Scheme 1).

Scheme 1. Proposed Aldol−Tishchenko Reaction with Sulfinimines



The classic aldol−Tishchenko reaction involves the self-addition of aldehydes with at least one α-hydrogen.[10] A similar reaction can occur between ketone enolates and 2 equiv of aldehyde. After the first addition, the formed aldolate reacts with the second equivalent of aldehyde, which is followed by stereoselective intramolecular hydride transfer to the C═O. Lithium enolates have been used to facilitate this transformation.[11]

The highly successful Evans−Tishchenko reaction involves the addition of an aldol adduct to an aldehyde in the presence of a Lewis acid,[12] although a generally applicable asymmetric variant of this reaction is lacking.[13] Seminal examples of asymmetric aldol−Tishchenko reactions include those by Mascarenhas,[14] Shibasaki,[15] and Mlynarski,[16] all of which utilized lanthanide complexes and chiral diol-based ligands.

Overall, the aldol−Tishchenko reaction has proven to be an excellent protocol for the preparation of 1,3-diol monoesters in a stereoselective manner and has been applied to a number of total syntheses.[17] To the best of our knowledge, no related strategy involving Tishchenko−hydride reduction of a C═N group has been reported, which is surprising given that the 1,3-amino alcohol precursors produced would be of great synthetic value.

The lack of precedence for this transformation probably reflects the difficulty in acquiring a suitable (aza)enolizable functionality along with lower electrophilicity of the C═N group negating hydride addition. For example, selected dimethyl hydrazones[18] and SAMP hydrazones[19] failed to undergo aldol−Tishchenko reactions in our hands. With this in mind, we proposed that sulfinimines may be more suitable substrates to facilitate an intramolecular Tishchenko hydride transfer due to the strong electron-withdrawing effects of the sulfinyl group, which greatly increases the electrophilicity of the C═N bond. Chiral *N*-sulfinimines[20] have a proven ability to form stable metalloenamines.[2] Furthermore, chirality about the sulfur would induce enantioselection.

We initiated our studies by preparing sulfinimines (*S*)-**1** and (*S*)-**2** from acetophenone and the corresponding *N*-sulfina-

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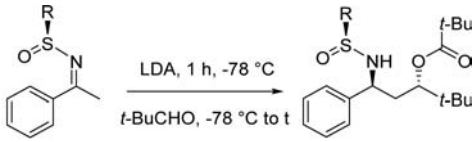
mide.[21] Deprotonation with LDA (−78 °C, 1 h) in THF was followed by the slow addition of 2.2 equiv of pivaldehyde and warming to room temperature overnight (Table 1). To our

Table 1. Optimization of the Aldol−Tishchenko Reaction



(*S*)-**1**, R = *t*-Bu
(*S*)-**2**, R = *p*-tolyl

3, R = *t*-Bu
4, R = *p*-tolyl

entry	s.m.	solvent	temp (°C)	*t*-BuCHO	yield (%)	dr[a]
1	**1**	THF	rt	2.2	41[b]	91:9
2	**2**	THF	rt	2.2	30[b]	78:22
3	**1**	toluene	rt	2.2	27[c]	80:20
4	**1**	ether	rt	2.2	22[c]	82:18
5[d]	**1**	THF	rt	2.2	22[b]	78:22
6	**1**	THF	0	2.2	48[c]	90:10
7	**1**	THF	0	3	69[c]	90:10
8	**1**	THF	−20	3	70[b]	91:9

[a]dr by NMR before purification. [b]Isolated. [c]Yield by NMR using 1,3,5-trimethoxybenzene as internal standard. [d]Reaction performed using $MgBr_2$ as additive.

delight, the aldol−Tishchenko products were formed (entries 1 and 2), albeit in moderate to poor yield (41% and 30%, respectively). However, the (*S*)-*tert*-butanesulfinimine gave an impressive dr (91:9), unlike its *p*-tolyl counterpart which gave a moderate dr (78:22).[22]

Therefore, we sought to optimize our procedure using sulfinimine (*S*)-**1**. A lower dr was observed in both toluene and ether (entries 3 and 4). Addition of $MgBr_2$[2c] also failed to give desirable results (entry 5). Lowering the temperature (entry 6) and addition of 3 equiv of aldehyde (entry 7) both gave improved yields. Further cooling to −20 °C and use of 3 equiv of aldehyde gave a good isolated yield of 70% and a dr of 91:9 (entry 8).

We then applied the optimized reaction conditions to a range of substituted aryl sulfinimines (**5**−**10**) as shown in Table 2 to afford the aldol−Tishchenko products **14**−**19**. Substrates with electron-donating (entries 1−3) and electron-withdrawing (entries 4 and 5) groups worked well, as did an acetonaphthone-derived sulfinimine (entry 6).

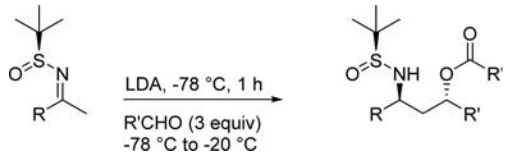
2-Furyl sulfinimine (entry 7) also worked well. Furthermore, alkyl sulfinimines which possess two possible sites for deprotonation showed complete regioselectivity for the least hindered site, affording products in moderate to excellent diastereoselectivity and excellent yield (entries 8 and 9).

Additionally, enolizable aldehydes, isobutyraldehyde, cyclohexane carboxaldehyde, and isovaleraldehyde were also effective, affording the corresponding amino alcohol derivatives (entries 10−13).[23] Having achieved acceptable results, we wondered if our methodology could be further challenged to perform the simultaneous introduction of three new stereogenic centers.

Surprisingly, there is no precedent in the literature, even for the reaction of metalloenamines derived from α-substituted sulfinimines with aldehydes (aldol).[24] Perhaps the potential for *E*- and *Z*-azenolate intermediates and the associated problems has deterred many research groups.

With this in mind, we chose a cyclic sulfinimine to initiate our tests. To our surprise, applying our optimized conditions to (*S*)-**27** using pivaldehyde and benzaldehyde (Scheme 2) gave the

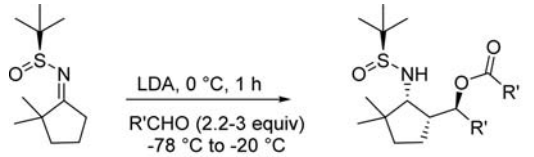
Table 2. Two New Chiral Centers: Substrate Scope



entry	s.m.	R	R′	product	yield[a] (%)	dr
1	**5**	*p*-MeC_6H_4	*t*-Bu	**14**	57	89:11
2	**6**	*m*-MeC_6H_4	*t*-Bu	**15**	64	89:11
3	**7**	*p*-$OMeC_6H_4$	*t*-Bu	**16**	65	90:10
4	**8**	*p*-FC_6H_4	*t*-Bu	**17**	62	96:4
5	**9**	*p*-$CF_3C_6H_4$	*t*-Bu	**18**	51	97:3
6	**10**	naphthyl	*t*-Bu	**19**	65	93:7
7	**11**	2-furyl	*t*-Bu	**20**	62	90:10
8	**12**	*i*-Pr	*t*-Bu	**21**	76	>97:3
9	**13**	Et	*t*-Bu	**22**	88	71:29[b]
10	**1**	C_6H_5	cyclohexyl	**23**	61	>97:3
11	**1**	C_6H_5	*i*-Pr	**24**	61	92:8
12	**8**	*p*-FC_6H_4	*i*-Pr	**25**	48	>97:3
13	**1**	C_6H_5	*i*-Bu	**26**	40	nd[c]

[a]Isolated. [b]Diastereomers could be separated by silica gel chromatography. [c]dr not determined due to the complexity of the NMR spectrum of the crude mixture. However, a single diastereomer was isolated in 40% yield.

Scheme 2. Formation of Three New Stereogenic Centers in One Pot



(*S*)-**27**

28, R' = *t*-Bu, 78%, *dr* 91:9
29, R' = Ph, 82%, *dr* >98:2

desired 1,3-amino alcohol derivatives in excellent diastereoselectivities (91:9 and >98:2) and yields (78% and 82%), respectively. To reiterate, in the case of benzaldehyde, one diastereomer (from a potential eight) was isolated in 82% yield.[25]

We next investigated propiophenone-based sulfinimine (*S*)-**30** with a range of aldehydes (Table 3).[26] The anticipated selectivity problems associated with *E*- and *Z*-azaenolates never manifested, and very good yields and dr values were obtained. In some cases, we noticed cleavage of the ester function, and thus, we applied base treatment in all these cases to isolate the 1,3-amino alcohol. Electron-rich (entries 1 and 5), electron-deficient (entries 2−4 and 7), and sterically bulky aryl aldehydes (entry 6) performed well, giving the desired products in very good diastereoselectivity (up to 88:9:3) and yields (up to 90%).

Notably, the intramolecular hydride transfer described herein allows for the preparation of 1,3-amino alcohols, such as **34**, containing a functional group which would be susceptible to reduction via an external reductant protocol.[27]

Crystallographic analysis of **31** and **33** revealed a 1,3-*anti* relative stereochemistry, and the 1,2 relative stereochemistry was assigned *syn*. Remarkably, however, a complete switch in absolute stereochemistry was observed in comparison to that observed for **3**.[28] We anticipate that the switch is general for propiophenone-based substrates.

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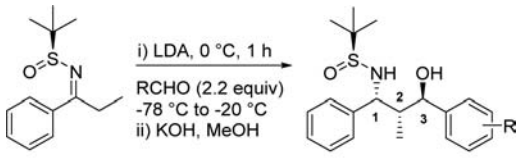
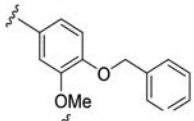
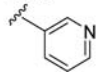
Table 3. Three New Chiral Centers: Substrate Scope



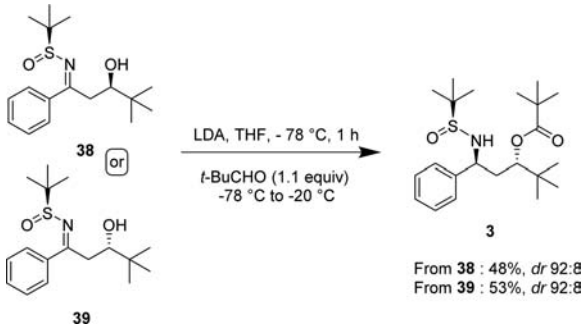
(*S*)-**30**

entry	s.m.	R	product	yield[a] (%)	*dr*[b]
1	**30**	H	**31**	87	86:14
2	**30**	*p*-F	**32**	90	88:9:3
3	**30**	*p*-Br	**33**	66	80:15:5
4	**30**	*p*-CN	**34**	52	82:18
5	**30**	*p*-OMe	**35**	74	86:9:5
6	**30**		**36**	66	83:9:8
7	**30**		**37**	52	83:12:5

[a]Isolated. [b]dr by NMR before purification.

To glean an insight into the reaction mechanism, a number of experiments were undertaken on the acetophenone-based substrate. First, the use of 1 equiv of aldehyde allowed for the isolation of both *syn*- and *anti*-disastereoisomers of the *β*-hydroxy-*N*-sulfinimines **38** and **39**. These were then separated and individually exposed to LDA and 1.1 equiv of pivaldehyde (Scheme 3). Only the *anti*-aldol−Tishchenko product **3** was

Scheme 3. Mechanistic Studies

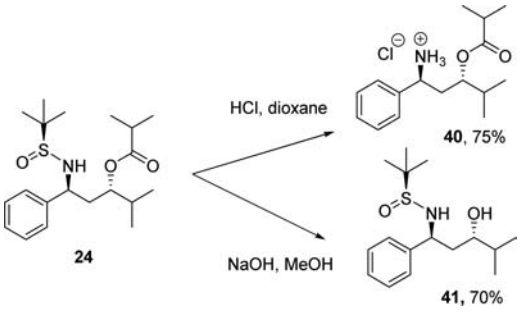


formed. In a similar reaction, involving the lithium aldolate of **38** but with addition of isobutyraldehyde, all four scrambled Tishchenko products were observed.[29] These results point to a reversible aldol reaction followed by a diastereo- and enantioselective nonreversible hydride transfer.

Finally, selective removal of each ancillary was easily achieved using HCl in dioxane (**41** to **40**) and NaOH in MeOH (**24**−**41**) (Scheme 4). The formation of the *anti*-1,3-amino alcohol moiety **41** compared favorably with Ellman's methodology which involved LDA and $MgBr_2$ (2 equiv) and Superhydride (2.5 equiv).[2c]

In summary, we described the first example of an aldol−Tishchenko reduction of a C═N group. More generally, we described a very rare example of the concomitant introduction of two (C−N, C−O) and three (C−N, C−C, C−O) chiral centers. Finally, highly useful 1,3-*anti*-amino alcohol precursors were acquired.

Scheme 4. Selective Ancillary Cleavage



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02919.

Experimental procedures, product characterizations, ^1H and ^{13}C NMR spectra for novel compounds, and X-ray crystallographic data for **3**, **31**, and **33** (PDF)

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Notes

The authors declare no competing financial interest.

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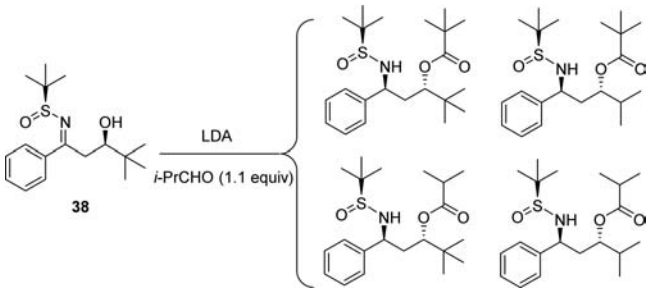
(22) The absolute stereochemistry of the major isomer was confirmed as *S*,*S*,*S* by degradation to known compounds and by crystallographic analysis. See the Supporting Information. The principle minor isomer was assigned as *S*,*R*,*R* by degradation to known compounds. In this case, the principle minor isomer presumably arises from a lack of selectivity of the chiral auxiliary rather than the aldol step or aldol−Tishchenko reduction step, specifically.
(23) Preliminary studies revealed that under the standard conditions described herein, benzaldehyde failed to give the corresponding aldol−Tishchenko product in good yield. Optimisation, in this case, is underway.
(24) Priede, M.; Kazak, M.; Kalnins, T.; Shubin, K.; Suna, E. *J. Org. Chem.* **2014**, *79*, 3715.
(25) The absolute stereochemistry of these products is unknown at this stage but is assigned here on the basis of the stereochemistry of the propiophenone-based substrates shown in Table 3.
(26) Preliminary studies revealed that under the standard conditions described herein isobutyraldehyde failed to give the corresponding aldol−Tishchenko product in good yield. Optimization, in this case, is underway.
(27) Furthermore, added 3-methoxybenzonitrile survived the aldol Tishchenko conditions and was not reduced. See Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597 for seminal use of this approach, and Supporting Information (S-92).
(28) The absolute stereochemistry of the major isomer was confirmed by degradation to known compounds and by crystallographic analysis. See the Supporting Information.
(29) Subsequent cleavage of the ester ancillaries in the below crude mixture gave a 53:47 mixture of the two expected amino alcohol derivatives. See the Supporting Information.



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