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Concise Asymmetric Synthesis of Orthogonally Protected *syn*- and *anti*-1,3-Aminoalcohols

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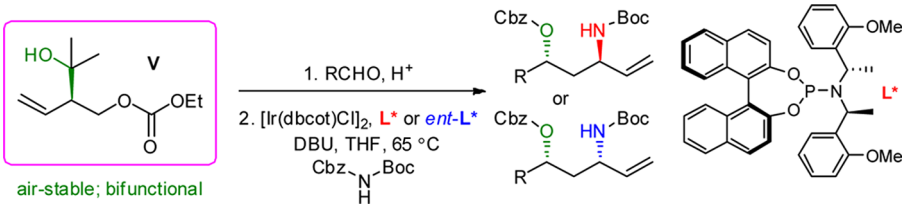
ABSTRACT



Novel chiral binfunctional reagents V and *ent*-V undergo asymmetric aldehyde allylation followed by Ir(I)-catalyzed enantioselective allylic amidation to give orthogonally protected *syn*- and *anti*-1,3-aminoalcohols with complete control of absolute and relative stereochemistry. The Mitsunobu reaction of the initial homoallylic alcohol products followed by Ir(I)-catalyzed enantioselective allylic amidation provides orthogonally protected *syn*- and *anti*-1,3-diamine derivatives in high yields and with excellent stereoselectivities.

The 1,3-amino alcohol motifs are common in many natural products and biologically active compounds.[1] 1,3-Aminoalcohols have also been used as chiral auxiliaries and ligands for asymmetric catalysis.[2] A vast majority of methods for their synthesis to date rely on diastereoselective reduction/addition of optically enriched β-hydroxy imine and β-amino ketone derivatives,[3] as well as diastereoselective C−H amination.[4] To our knowledge, only a few enantioselective methods are currently available, which include rhodium-catalyzed asymmetric hydrogenation of β-ketoenamides,[5] a proline-catalyzed enantioselective Mannich reaction followed by tandem hydrogenation–enzymatic dynamic kinetic resolution,[6] and a strategy employing proline-catalyzed α-aminoxylation and α-amination of aldehydes for the asymmetric introduction of C−O/N

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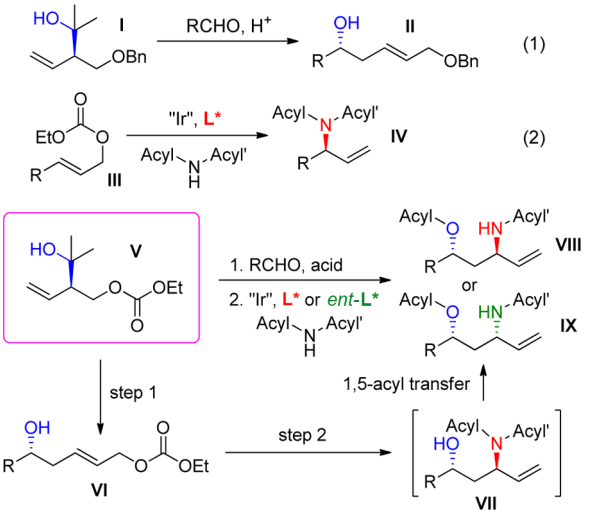
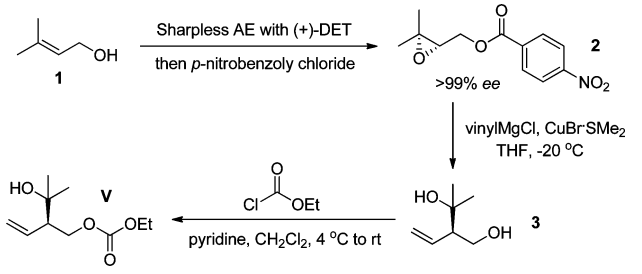
bonds.[7] Although these methods can deliver 1,3-aminoalcohols in a stereoselective fashion, they require multiple steps and/or suffer from a limited substrate scope.[8] Furthermore, rhodium-catalyzed asymmetric hydrogenation of β-ketoenamides gives rise to only *anti*-1,3-aminoalcohols. Remarkably, very efficient enantioselective methods to give orthogonally protected 1,3-aminoalcohols with complete control of their relative and absolute stereochemistry remain undeveloped. Herein we report a conceptually distinct method for the very efficient asymmetric synthesis of orthogonally protected *syn*- and *anti*-1,3-aminoalcohols, which utilizes newly developed air-stable chiral binfunctional allylation reagents **V** and *ent*-**V** (Scheme 1).

Scheme 1. Design Concept of Chiral Bifunctional Reagent **V** for the Asymmetric Synthesis of Orthogonally Protected *syn*- and *anti*-1,3-Aminoalcohols



Recently the Nokami group reported that, in the presence of an acid, enantioenriched tertiary homoallylic alcohol **I** could react with aldehydes through [3,3]-sigmatropic rearrangement to deliver homoallylic alcohols **II** with near-perfect chirality transfer and high *E*/*Z*-selectivity (eq 1 in Scheme 1).[9,10] We and others recently disclosed Ir(I)-catalyzed enantioselective allylic amidation between ethyl allyl carbonates **III** and diacylamine nucleophiles to give protected allylic amines **IV** (eq 2 in Scheme 1).[11,12] A logical extension of these two observations would be to combine Nokami's allyl transfer reaction with the Ir(I)-catalyzed allylic amidation reaction to create a new chiral bifunctional reagent **V**. As shown in Scheme 1, asymmetric allylation of aldehydes by **V** is expected to give allyl carbonates **VI**. Ir(I)-catalyzed allylic amidation of **VI** with diacylamine nucleophiles will initially generate the intermediates **VII**, which could undergo an intramolecular 1,5-acyl transfer reaction under the appropriate allylic amidation conditions to finally give orthogonally protected 1,3-aminoalcohols **VIII** and **IX**. If the stereochemistry of the amidation step is governed by the chiral ligands **L*** or *ent*-**L*** used, the presented two-step strategy can provide a most direct method for the asymmetric synthesis of orthogonally protected 1,3-aminoalcohols from the readily available aldehydes with complete control of their relative and absolute stereochemistry.

Scheme 2. Asymmetric Synthesis of Enantiomerically Pure Bifunctional Allyl Transfer Reagent **V**



Enantiomerically pure binfunctional reagents **V** and *ent*-**V** were conveniently prepared from commercial 3-methylbuten-2-en-1-ol in three steps (Scheme 2). Sharpless asymmetric epoxidation (AE) of 3-methylbuten-2-en-1-ol (**1**) by (+)-diethyl tartrate (DET) gave rise to the corresponding 2-epoxy alcohol, which was isolated as its *p*-nitrobenzoate ester **2**.[9] Enantiomerically pure **2** (*ee* > 99%) was obtained by washing crude **2** with ethyl ether. Reaction of **2** with vinylMgCl in the presence of $CuBr \cdot SMe_2$ at −20 °C furnished diol **3**,[9] which upon treatment with ethyl chloroformate and pyridine transformed into **V**. The same reaction sequence using (−)-DET in the Sharpless AE step was used to prepare *ent*-**V**. Binfunctional reagents **V** and *ent*-**V** are stable at ambient temperature and can be stored without any special precautions.

(8) Reference 5 works only for the terminal methyl group and gives only an (*R*)-configuration at the oxygen-substituted carbon due to the substrate specificity of the enzyme CALB used; ref 6 requires preparation of β-ketoenamides from the corresponding ketones in two steps; ref 7 requires five to six steps to prepare 1,3-aminoalcohol derivatives.

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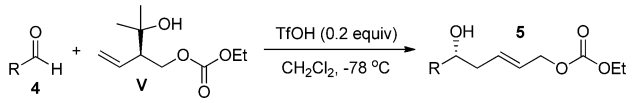
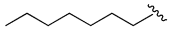
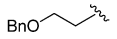
Table 1. Asymmetric Allyl Transfer Reaction between Aldehydes **4** and Chiral Bifunctional Reagent **V**



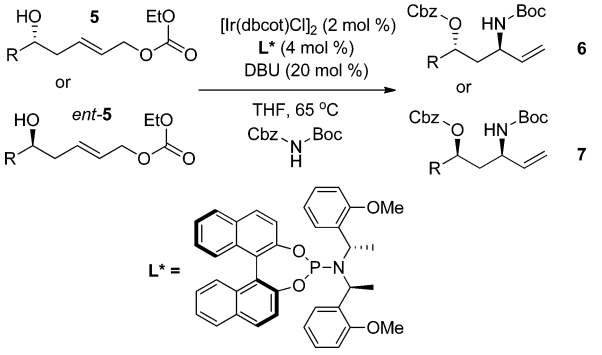
entry	R-	product	yield [%][a]	*ee* [%][b]
1		(*S*)-**5a**	90	99
2		(*R*)-**5b**	78	98
3		(*R*)-**5c**	82	99
4		(*S*)-**5d**	75	99
5		(*R*)-**5e**	74	99
6		(*R*)-**5f**	76	98
7		(*R*)-**5g**	86	99

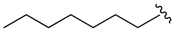
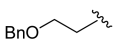
[a] Isolated yields. [b] Determined by chiral HPLC.

Acid-mediated asymmetric allylation of *n*-octanal by **V** was used to determine the optimal conditions. After screening various acids (TfOH, TMSOTf, trifluoromethanesulfonimide, 2,4-dinitrobenzenesulfonic acid, (1*S*)-(+)-camphorsulfonic acid, *p*-TsOH·H_2O, $TiCl_4$, $Sc(OTf)_3$, and $BF_3{\cdot}OEt_2$) and temperatures (−78, −50, −20, and 0 °C) in methylene chloride, the reaction conditions involving 0.2 equiv of TfOH at −78 °C were determined to be optimal to give the corresponding homoallylic ether **5a** in 90% reaction yield and 99% *ee*. A selection of aldehydes were allowed to react with **I** under the determined reaction conditions, and the results are shown in Table 1. The asymmetric allyl transfer reaction tolerated wide structural variations in aldehydes involving linear alkyl (entry 1), *β*-branched alkyl (entry 2), α-branched alkyl (entries 3 and 4), cycloalkyl (entry 5), *tert*-butyl (entry 6), and functionalized linear alkyl (entry 7) groups. The corresponding homoallylic alcohols **5** were obtained in good yields up to 90%, and chirality transfer was nearly perfect to give ≥98% *ee*'s. In all cases studied, only *E*-**5** formed as judged by NMR analysis; the *E*-geometry is necessary for Ir(I)-catalyzed enantioselective allylic amidation.

To study Ir(I)-catalyzed diastereoselective allylic amidation, **5a** was subjected to the catalytic conditions involving $[Ir(COD)Cl]_2$ (2 mol %), **L*** (4 mol %), DBU (20 mol %), and benzyl *tert*-butyl imidodicarboxylate as a nucleophile in THF.[11f,13] However, the desired allylic amidation reaction did not occur even under heating conditions with higher ligand loadings. Based on the premise that $[Ir(dbcot)Cl]_2$ could generate more robust catalysts than $[Ir(COD)Cl]_2$,[14] 2 mol % $[Ir(dbcot)Cl]_2$ was used at rt. The ethyl allyl carbonate **5a** did not react at rt, but upon raising the temperature to 65 °C, the reaction proceeded cleanly to give *O*-Cbz, *N*-Boc protected 1,3-aminoalcohol **6a** in 85% yield and with >20:1 diastereoselectivity. On the other hand, under the same conditions, *ent*-**5a** provided the corresponding diastereomer **7a** in 88% yield and with >20:1 diastereoselectivity (Table 2, entries 1 and 2). Similarly, other structurally diverse **5** and *ent*-**5** compounds (which were prepared by using *ent*-**V** and aldehydes **4** as in Table 1) provided the corresponding *O*-Cbz, *N*-Boc protected 1,3-aminoalcohols **6** and **7**, respectively, in good yields and with excellent diastereoselectivities. These results indicate that the stereochemistry of the allylic amidation is predominantly controlled by the stereochemistry of the ligand/catalyst used, and 1,5-acyl transfer takes place under the amidation conditions.

Table 2. Ir(I)-Catalyzed Diastereoselective Allylic Amidation of Homoallylic Alcohols **5** and *ent*-**5**



entry	R-	alcohol	product	yield [%][a]	dr[b]
1		(*S*)-**5a**	(*3R, 5S*)-**6a**	85	>20:1
2		*ent*-**5a**	(*3R, 5R*)-**7a**	88	>20:1
3		(*S*)-**5b**	(*3R, 5S*)-**6b**	81	>20:1
4		*ent*-**5b**	(*3R, 5R*)-**7b**	84	>20:1
5		(*R*)-**5c**	(*3R, 5R*)-**6c**	80	>20:1
6		*ent*-**5c**	(*3R, 5S*)-**7c**	82	>20:1
7		(*R*)-**5e**	(*3R, 5R*)-**6e**	79	>20:1
8		*ent*-**5e**	(*3R, 5S*)-**7e**	83	>20:1
9		(*R*)-**5f**	(*3R, 5R*)-**6f**	83	>20:1
10		*ent*-**5f**	(*3R, 5S*)-**7f**	85	>20:1
11		(*R*)-**5g**	(*3R, 5R*)-**6g**	85	>20:1
12		*ent*-**5g**	(*3R, 5S*)-**7g**	87	>20:1

[a] Isolated yields. [b] Determined by the ^1H NMR spectrum of reaction mixtures.

To further demonstrate the synthetic utility of homoallylic alcohols **5** and *ent*-**5**, we chose to transform

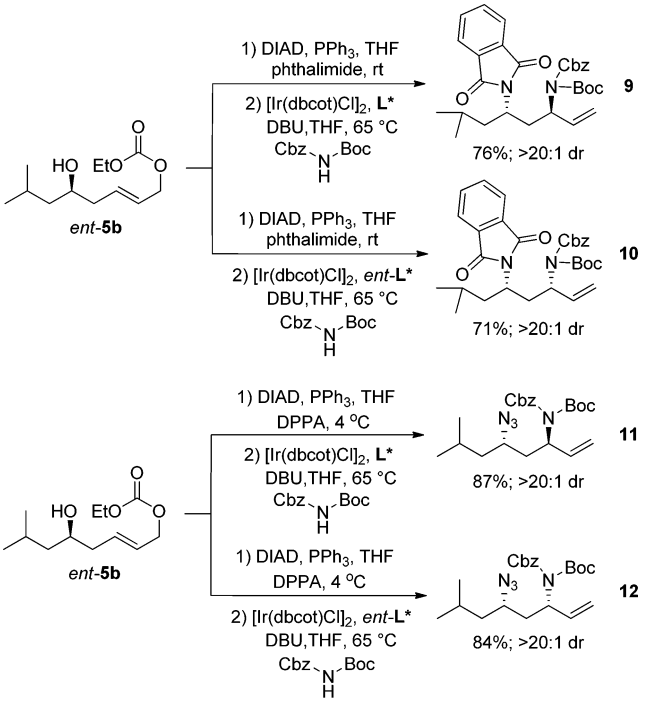
(13) $(Cbz)_2NH$, $(Boc)_2NH$, and phthalimide were tried, but the desired allylic amidation did not occur. AcNHBoc gave rise to a mixture of amidation product and 1,5-acyl transfer product.

(14) Spiess, S.; Welter, C.; Frank, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7652–7655.

ent-**5b** into the corresponding 1,3-diamine derivatives. 1,3-Diamine functionalities are a key structural element in numerous natural products and pharmacologically active compounds,[15] as well as chiral ligands for asymmetric catalysis.[16] Despite recent synthetic advancements, methods for the asymmetric synthesis of 1,3-diamines via enantioselective processes have been severely underdeveloped.[17] Scheme 3 describes the two-step asymmetric synthesis of orthogonally protected 1,3-diamines from *ent*-**5b**. The Mitsunobu reaction between homoallylic alcohol *ent*-**5b** (entry 4, Table 2) and phthalimide furnished the corresponding homoallylic amine,[18,18b] which upon Ir(I)-catalyzed allylic amidation in the presence of **L*** transformed into orthogonally protected 1,3-diamine **9** in 76% overall yield and with > 20:1 dr as judged by NMR analysis. The same reaction sequence using *ent*-**L*** for the allylic amidation delivered the corresponding diastereomer **10** in 71% overall yield and with > 20:1 dr. Similarly, homoallylic alcohol *ent*-**5b** was converted into diastereomeric azides **11** and **12** by using diphenyl phosphoryl azide (DPPA)[18c,d] in the Mitsunobu reaction in 87% and 84% overall yields, respectively, and with > 20:1 dr.

In conclusion, novel chiral bifunctional reagents **V** and *ent*-**V**, which are air-stable and can be used in a step-economical fashion, have been developed. The reagents undergo asymmetric aldehyde allylation followed by Ir(I)-catalyzed allylic amidation to deliver orthogonally protected *syn*- and *anti*-1,3-aminoalcohols in good yields and with excellent stereoselectivities. The synthetic utility of **V** was further demonstrated in the three-step asymmetric synthesis of orthogonally protected 1,3-diamine derivatives. Considering the importance and prevalence of 1,3-aminoalcohol and 1,3-diamine motifs in numerous (bio)chemically active molecules, the developed strategies employing **V** and *ent*-**V** should find wide synthetic applications.

Scheme 3. Asymmetric Synthesis of 1,3-Diamine Derivatives



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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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