

# 1,3-Dipolar Cycloadditions of Carbonyl Ylides to Aldimines: Scope, Limitations and Asymmetric Cycloadditions

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**Abstract:** The development of a diastereoselective 1,3-dipolar cycloaddition of carbonyl ylides and imines for the synthesis of  $\alpha$ -hydroxy- $\beta$ -amino esters is described. The methodology is successfully applied to chiral  $\alpha$ -methylbenzylimines affording enantio-merically pure *syn*- $\beta$ -amino alcohols, which is exemplified with a short asymmetric synthesis of the paclitaxel side-chain. The use of chiral Rh(II) carboxylate

catalysts for the development of a catalytic enantio-selective 1,3-dipolar cycloaddition is also described, affording *syn*- $\beta$ -amino alcohols in modest enantio-meric purity (*e.r.* up to 82:18).

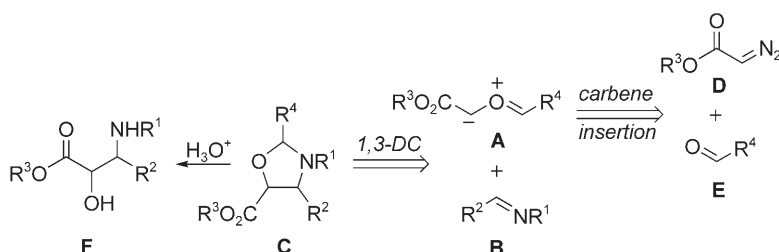
**Keywords:** amino alcohols; asymmetric 1,3-dipolar cycloadditions; carbenoids; carbonyl ylides; imines; multicomponent reactions

## Introduction

The  $\beta$ -amino alcohol and the  $\alpha$ -hydroxy- $\beta$ -amino acid moieties are found in a vast array of biologically important compounds and as a result these structural subunits are frequently used as building blocks in natural product synthesis.<sup>[1]</sup> Moreover, the  $\beta$ -amino alcohol functionality also serves as a chiral ligand and auxiliary, which has a broad application in asymmetric synthesis and catalysis.<sup>[2]</sup> Consequently, considerable efforts have been made to develop asymmetric routes to enantiopure  $\beta$ -amino alcohols.<sup>[3]</sup> The amino alcohol functionality is most commonly introduced on a pre-existing carbon skeleton, which can be accomplished by Sharpless aminohydroxylation<sup>[4]</sup> or by the opening of epoxides<sup>[3,5,6]</sup> and aziridines<sup>[3,6,7]</sup> with appropriate nucleophiles. More effectively, the amino alcohol moiety can be constructed by concomitant formation of a new carbon-carbon bond and two vicinal stereo-

genic centers in a single step. This approach has been realized by addition of glycine-derived enolates to aldehydes<sup>[1b,8]</sup> or by addition of  $\alpha$ -alkoxy enolates to aldimines in a Mannich-type reaction.<sup>[1a,9]</sup>

In recent years multi-component 1,3-dipolar cycloadditions involving ylides derived from transiently formed carbenoid intermediates have received considerable attention since this constitutes a powerful tool for constructing five-membered heterocycles.<sup>[10]</sup> Surprisingly, to our knowledge very few examples of cycloadditions involving carbonyl ylides and imines have previously been reported.<sup>[11]</sup> With this in mind, it was envisioned that 1,3-dipolar cycloadditions of stabilized carbonyl ylides (**A**) to imines (**B**) would be an efficient entry to functionalized oxazolidines (**C**, Scheme 1). The carbonyl ylide **A**, in turn, should be available from diazo ester **D** and aldehyde **E**. Hydrolysis of the *N,O*-acetal **C** would ultimately yield the desired  $\beta$ -amino alcohol **F**. The realization of this

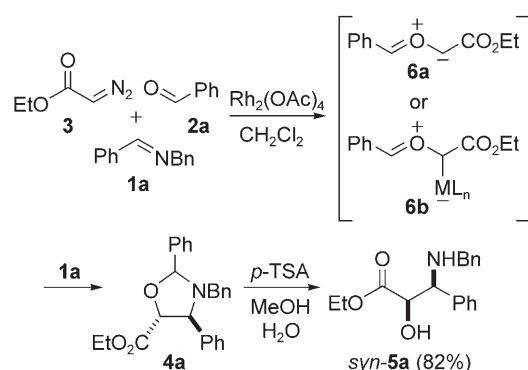


**Scheme 1.** Synthetic strategy.

three-component strategy for the synthesis of *syn*- $\alpha$ -hydroxy- $\beta$ -amino esters and its application to the asymmetric synthesis of the C-13 paclitaxel side-chain was recently reported from our laboratory.<sup>[12]</sup> Herein we report our full investigation of this asymmetric three-component approach for the synthesis of *syn*- $\alpha$ -hydroxy- $\beta$ -amino esters using both chiral imines and chiral Rh(II) catalysts.

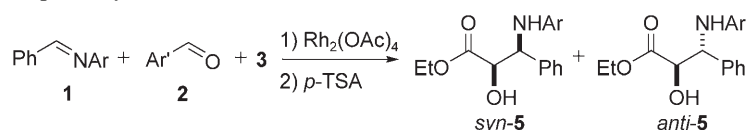
## Results and Discussion

The reaction was initially explored using commercial-ly available benzylidene-benzylamine (**1a**), benzalde-



**Scheme 2.** 1,3-Dipolar cycloaddition.

**Table 1.** Optimization of 1,3-dipolar cycloaddition.



Entry	1 (Ar)	2 (Ar')	Cat.	<i>dr</i> <sup>[b]</sup> <i>syn:anti</i>	Yield <sup>[c]</sup> <b>5</b> (%)
1	<b>a</b> (Bn)	<b>a</b> (Ph)	Rh <sub>2</sub> (OAc) <sub>4</sub>	93:7	<b>a</b> (82)
2	<b>a</b> (Bn)	<b>a</b> (Ph)	Rh <sub>2</sub> (pfb) <sub>4</sub>	88:12	<b>a</b> (13)
3	<b>a</b> (Bn)	<b>a</b> (Ph)	Cu(OTf) <sub>2</sub>	N.A.	<b>a</b> (0) <sup>[d]</sup>
4 <sup>[e]</sup>	<b>a</b> (Bn)	<b>a</b> (Ph)	Rh <sub>2</sub> (OAc) <sub>4</sub>	67:33	<b>a</b> (67)
5 <sup>[f]</sup>	<b>a</b> (Bn)	<b>a</b> (Ph)	Rh <sub>2</sub> (OAc) <sub>4</sub>	64:36	<b>a</b> (70)
6	<b>b</b> (Ph)	<b>a</b> (Ph)	Rh <sub>2</sub> (OAc) <sub>4</sub>	N.A.	<b>b</b> (0) <sup>[g]</sup>
7	<b>c</b> (4-MeO-C <sub>6</sub> H <sub>4</sub> )	<b>a</b> (Ph)	Rh <sub>2</sub> (OAc) <sub>4</sub>	N.A.	<b>c</b> (0) <sup>[d]</sup>
8 <sup>[h]</sup>	<b>d</b> (Ts)	<b>a</b> (Ph)	Rh <sub>2</sub> (OAc) <sub>4</sub>	n.d.	<b>d</b> (19) <sup>[i]</sup>
9	<b>a</b> (Bn)	<b>b</b> (4-MeO-C <sub>6</sub> H <sub>4</sub> )	Rh <sub>2</sub> (OAc) <sub>4</sub>	80:20	<b>a</b> (67)
10	<b>a</b> (Bn)	<b>c</b> (4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> )	Rh <sub>2</sub> (OAc) <sub>4</sub>	85:15	<b>a</b> (47)

<sup>[a]</sup> The reaction was carried out with imine **1** (1.0 equiv.), benzaldehyde (1.5 equivs.), Rh catalyst (2.0 mol %) or Cu(OTf)<sub>2</sub> (5 mol %) and powdered 4 Å MS in CH<sub>2</sub>Cl<sub>2</sub> (Rh catalyst) or THF (Cu catalyst) at room temperature with addition of ethyl diazoacetate (1.5 equivs.) over 1 h.

<sup>[b]</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture, *syn*- and *anti*-diastereomers separable with flash chromatography.

<sup>[c]</sup> Isolated yield (*syn* and *anti*).

<sup>[d]</sup> Only starting material.

<sup>[e]</sup> Cu(OTf)<sub>2</sub> (5 mol %) present.

<sup>[f]</sup> Yb(OTf)<sub>3</sub> (5 mol %) present.

<sup>[g]</sup> Complicated mixture of by-products.

<sup>[h]</sup> Performed at 45 °C.

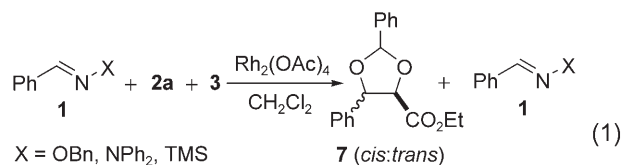
<sup>[i]</sup> Ratio **5d:7** = 40:60.

hyde (**2a**) and Rh<sub>2</sub>(OAc)<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 2). Addition of ethyl diazoacetate (EDA, **3**) over 1 h at room temperature afforded the desired cycloadduct **4**, which upon hydrolysis yielded  $\beta$ -amino alcohol **5a** (*syn:anti* 93:7) in 82 % yield (*syn*) (Table 1, entry 1). The relative stereochemistry of **5a** was verified by conversion into the corresponding oxazolidinone followed by <sup>1</sup>H NMR analysis of the relevant coupling constants.<sup>[13]</sup>

Mechanistically, the reaction is likely to proceed through a chemoselective insertion of the electrophilic Rh-metallocarbene into the lone pair of benzaldehyde forming either a metal-free<sup>[10a,14a]</sup> (**6a**) or a metal-associated ylide<sup>[14]</sup> (**6b**), which then undergoes a 1,3-dipolar cycloaddition with the aldimine yielding *trans*-substituted oxazolidine **4a**.

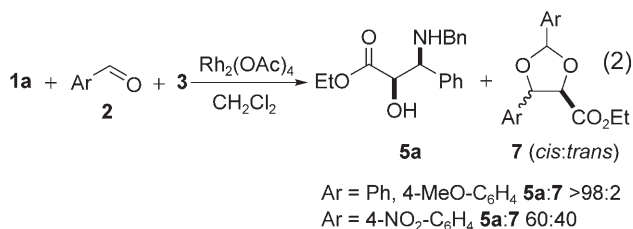
It was then of interest to optimize the key components of the reaction. First the choice of metal catalyst used for the diazo decomposition was examined. Rh<sub>2</sub>(pfb)<sub>4</sub>, used in a variety of carbenoid reactions, gave the desired product albeit with diminished yield and diastereoselectivity (Table 1, entry 2). Cu(OTf)<sub>2</sub>, commonly used as a suitable catalyst for the decomposition of **3**, only led to recovery of **1a** (entry 3), the reason probably being coordination of the metal to the basic imine nitrogen with concomitant inhibition of the carbenoid formation.<sup>[10c,d,15]</sup> In order to investigate if a Lewis acid activation of the imine would in-

fluence the reaction outcome, Cu(OTf)<sub>2</sub> and Yb(OTf)<sub>3</sub> were added to the reaction mixture (entries 4 and 5). In both cases the desired product was obtained in good yield but with moderate diastereoselectivity. This change in reaction outcome indicated that a complexation between the Lewis acid and imine had indeed occurred. Next, a variety of different *N*-substituted imines was screened, which proved to have a large impact on the reaction outcome. When using imine **1b**, derived from aniline, a complex reaction mixture was obtained with no trace of the desired product (entry 6), while attempts with **1c** only gave recovered starting material (entry 7). Heteroatom substituents, for example, oxime ethers, hydrazones and *N*-trialkylsilylimines, only lead to the formation of the corresponding 1,3-dioxolane **7** via a 1,3-dipolar cycloaddition in which the aldehyde also served as a dipolarophile [Eq. (1)].<sup>[10a,b]</sup> Apart from



*N*-benzyl-substituted imines, only *N*-sulfonylimine **1d** lead to the formation of the desired product, although only as the minor product along with substantial amounts of dioxolane **7** (entry 8). Exchanging benzaldehyde (**2a**) for other aromatic aldehydes (4-MeO-C<sub>6</sub>H<sub>4</sub> and 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>) did not improve the reaction outcome and thus the remaining experiments were performed with **2a** (entries 9 and 10).

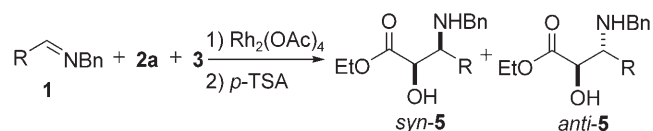
Interestingly, when 4-nitrobenzaldehyde was used as the aldehyde component significant amounts of dioxolane **7** were formed [Eq. (2)]. In this case the elec-



tron-deficient 4-nitrobenzaldehyde also served as a dipolarophile. This side product was not detected in the case of benzaldehyde or 4-methoxybenzaldehyde.

With optimized reaction conditions at hand, the performance of other *N*-benzyl-substituted aldimines was investigated and the results are summarized in Table 2. In all cases, the reaction proceeded cleanly to provide the desired *syn*-β-amino alcohol in high yield

**Table 2.** 1,3-Dipolar cycloaddition to benzylimines.<sup>[a]</sup>



Entry	<b>1</b> (R)	<i>dr</i> <sup>[b]</sup> ( <i>syn:anti</i> )	Yield <sup>[c]</sup> <i>syn</i> - <b>5</b> (%)
1	<b>a</b> (Ph)	93:7	<b>a</b> (82)
2 <sup>[d]</sup>	<b>e</b> (4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> )	91:9	<b>e</b> (61)
3	<b>f</b> (4-Cl-C <sub>6</sub> H <sub>4</sub> )	98:2	<b>f</b> (75)
4	<b>g</b> (4-F-C <sub>6</sub> H <sub>4</sub> )	97:3	<b>g</b> (78)
5	<b>h</b> (3-MeO-C <sub>6</sub> H <sub>4</sub> )	98:2	<b>h</b> (77)
6	<b>i</b> (4-Me-C <sub>6</sub> H <sub>4</sub> )	97:3	<b>i</b> (87)
7 <sup>[d]</sup>	<b>j</b> (4-MeO-C <sub>6</sub> H <sub>4</sub> )	94:6	<b>j</b> (78)
8	<b>k</b> (2-naphthyl)	98:2	<b>k</b> (83)
9 <sup>[d,e]</sup>	<b>l</b> (2-furyl)	92:8	<b>l</b> (75)
10 <sup>[d,e]</sup>	<b>m</b> (CO <sub>2</sub> Et)	81:17	<b>m</b> (64)

[a] The reaction was carried out with imine **1** (1.0 equiv.), benzaldehyde (1.5 equivs.), Rh<sub>2</sub>(OAc)<sub>4</sub> (2.0 mol %) and powdered 4 Å MS in CH<sub>2</sub>Cl<sub>2</sub> at room temperature with addition of ethyl diazoacetate (1.5 equivs.) over 1 h.

[b] Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture, *syn*- and *anti*-diastereomers separable with flash chromatography.

[c] Isolated yield.

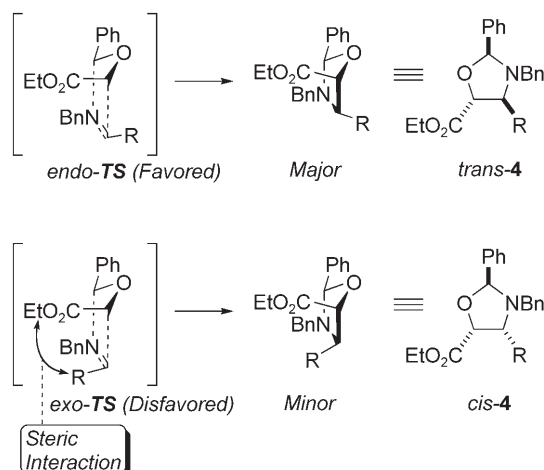
[d] 10 h addition time.

[e] 0 °C.

and excellent diastereoselectivity irrespective of the steric or electronic properties of the aryl substituent (entries 1–8).<sup>[16]</sup> The furfural-derived imine **1l** afforded the corresponding product **5l** in high yield and diastereoselectivity (entry 9), which is of interest since the furan moiety can be readily derivatized into several useful functional groups.<sup>[17,18]</sup> The reaction of ethyl glyoxalate imine **1m** gave the *syn*-β-hydroxyaspartate **5m**, a potent blocker of the glutamate transporters<sup>[19]</sup>, in high yield and good diastereoselectivity (entry 10). It should be noted that imines derived from aliphatic aldehydes did not react under these reaction conditions.

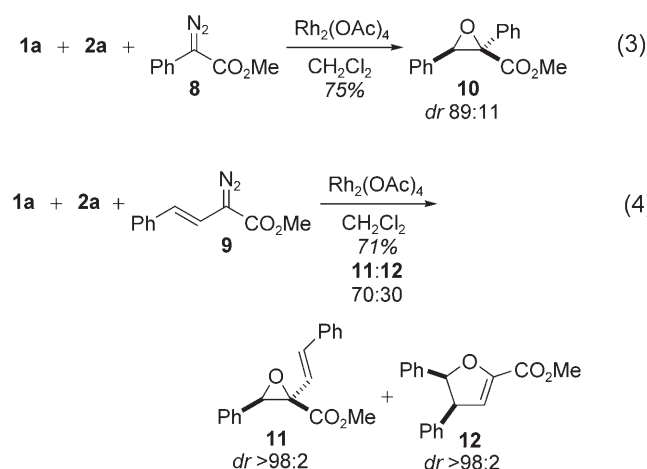
The observed *syn*-diastereoselectivity can be explained by invoking an envelope-type transition state where the thermodynamically most stable S-shaped ylide<sup>[14a]</sup> reacts with the imine in an *endo*-selective cycloaddition favoring the formation of *trans*-oxazolidine **4** (Scheme 3). The *endo*-transition state is favored over the *exo*-transition state due to the steric interaction between the ester functionality on the ylide and the benzylidene substituent on the imine.

During the last couple of years it has been recognized that the diazoacetate structure has a large impact on the reaction outcome.<sup>[20]</sup> The most pronounced effect was found for diazoacetates functionalized with electron-donating groups, for example, vinyl and aryl. It has been shown independently by the groups of Davies<sup>[21]</sup> and Doyle<sup>[22]</sup> that Rh-cata-



**Scheme 3.** Proposed stereochemical model for the 1,3-dipolar cycloaddition.

lyzed decomposition of donor/acceptor diazoacetates in the presence of aldehydes leads to the formation of epoxides and dihydrofurans through intramolecular ring closure of the transient carbonyl ylide. This is in contrast to the behavior of EDA, which forms 1,3-dioxolanes through 1,3-dipolar cycloadditions. The reaction between donor/acceptor diazoacetates **8** and **9** with imine **1a** and aldehyde **2a** gave, unfortunately, no traces of the desired products [Eq. (3) and Eq. (4)]; in-

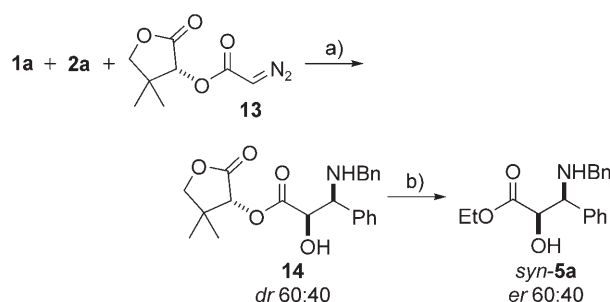


stead epoxide **10** (from **8**) and a mixture of epoxide **11** and dihydrofuran **12** (from **9**) were isolated in comparable yields and selectivities as previously reported.

## Asymmetric 1,3-Dipolar Cycloadditions

### Chiral diazo esters

It was also of interest to develop an asymmetric protocol for the synthesis of enantiomerically enriched

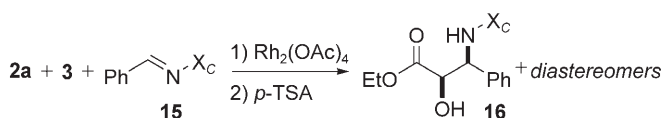


**Scheme 4.** 1,3-Dipolar cycloaddition using pantolactone diazo ester. *Reagents and conditions:* a) 1)  $\text{Rh}_2(\text{OAc})_4$  (2 mol %), 4 Å MS,  $\text{CH}_2\text{Cl}_2$ , 0°C; 2) *p*-TSA,  $\text{MeOH}/\text{H}_2\text{O}$  (95:5), room temperature (82%, *dr* 60:40); b)  $\text{Ti}(\text{O}-i\text{-Pr})_4$ , EtOH, PhMe, 110°C (60%, *er* 60:40).

*syn*- $\beta$ -amino alcohols and ultimately apply it to the synthesis of biologically active natural products. Initial attempts with (–)-8-phenylmenthyl diazoacetate<sup>[23]</sup> as the carbene source together with **1a** and **2** gave none of the desired product. The chiral diazoacetate **13**, derived from (*R*)-pantolactone,<sup>[24]</sup> has been reported to give good results when used in asymmetric cyclopropanations<sup>[25]</sup> and aziridinations.<sup>[26]</sup> Unfortunately, when tested under the standard reaction conditions only a modest asymmetric induction was obtained (Scheme 4). The desired amino alcohol **14** was isolated in high yield as a 60:40 mixture of two diastereomers (absolute configuration was not determined).<sup>[27]</sup> In order to determine the relative stereochemistry of the product, the mixture was subjected to a  $\text{Ti}(\text{O}-i\text{-Pr})_4$ -catalyzed transesterification protocol,<sup>[28]</sup> which gave the known amino alcohol *syn*-**5a** as single diastereomer indicating that the relative stereochemistry of **14** was *syn*. The enantiomeric ratio of *syn*-**5a** (*er* 60:40) was in good agreement with the diastereomeric ratio of **14** (*dr* 60:40).

### Chiral imines

Since the use of chiral diazo esters only met with limited success we became interested in investigating chiral imines, a strategy that has been successfully applied in other cycloaddition reactions.<sup>[29]</sup> Consequently, chiral imine **15a**, derived from (+)- $\alpha$ -methylbenzylamine, was reacted under standard conditions, which led to the formation of amino alcohol **16a** in high yield and diastereoselectivity (8.2:1:1:0) (Table 3, entry 1). The major diastereomer was readily separated from the two minor diastereomers using flash chromatography. The relative stereochemistry of the major product was determined to be *syn* by conversion into the corresponding oxazolidinone followed by  $^1\text{H}$  NMR analysis of the relevant coupling constants.<sup>[30]</sup>

**Table 3.** Optimization of 1,3-dipolar cycloaddition using chiral imines<sup>[a]</sup>

Entry	<b>15</b> ( $\text{X}_c$ )	Lewis acid	$dr^{[b]}$	Yield <sup>[c]</sup> <b>16</b> (%)
1	<b>a</b>	none	8.2:1:1:0	<b>a</b> (77)
2	<b>b</b>	none	n.d.	<b>b</b> (traces)
3	<b>c</b>	none	n.d.	<b>7</b> (n.d.)
4	<b>d</b>	none	n.d.	<b>7</b> (n.d.)
5	<b>d</b>	$\text{Yb}(\text{OTf})_3$	3.6:3:1.7:1	<b>d</b> (75) <sup>[d]</sup>
6	<b>d</b>	$\text{Zn}(\text{OTf})_2$	3:2.7:1.9:1	<b>d</b> (93) <sup>[d]</sup>

<sup>[a]</sup> The reaction was carried out with imine **15** (1.0 equiv.), benzaldehyde (1.5 equivs.),  $\text{Rh}_2(\text{OAc})_4$  (2.0 mol %) and powdered 4 Å MS in  $\text{CH}_2\text{Cl}_2$  at 0°C with addition of ethyl diazoacetate (1.5 equivs.) over 10 h.

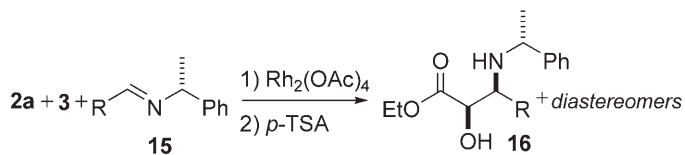
<sup>[b]</sup> Determined by  $^1\text{H}$  NMR spectroscopic analysis of the crude reaction mixture.

<sup>[c]</sup> Isolated yield (all isomers).

<sup>[d]</sup> Isomers not separable with flash chromatography.

Several other commonly used chiral imines were also screened in order to improve the results, but this met with no success (Table 3). When chiral imine **15d**, derived from phenylalanine, was employed only dioxolane **7** could be detected with no trace of the desired product. Interestingly, when a Lewis acid was added to the reaction mixture, amino alcohol **16d** was isolated as the sole product in high yield although as an inseparable mixture of all four possible diastereomers (entries 5 and 6).

The performance of other imines derived from (+)- $\alpha$ -methylbenzylamine is summarized in Table 4. For all aromatic substrates the reaction proceeded cleanly to give the desired *syn*-product in high yield and diastereoselectivity (entries 1–6), and in all cases the major isomer was separable from the mixture of the two minor isomers using flash chromatography. It should be noted that the reaction also proceeded cleanly when conducted on a multigram-scale (2–4 g of imine *ent*-**15f**, entry 4). Furthermore, chiral imine **15j**, derived from ethyl glyoxalate, gave the product in good yield and diastereoselectivity (entry 8). However, reaction of 2-furylimine **15i** under standard con-

**Table 4.** 1,3-Dipolar cycloaddition to (+)- $\alpha$ -methylbenzyl imines<sup>[a]</sup>

Entry	<b>15</b> (R)	$dr^{[b]}$	Yield <sup>[c]</sup> <b>16</b> (%)
1	<b>a</b> (Ph)	8.2:1:1:0	<b>a</b> (77)
2	<b>e</b> (4-MeO-C <sub>6</sub> H <sub>4</sub> )	5.4:1:1:0	<b>e</b> (86)
3	<b>f</b> (3-MeO-C <sub>6</sub> H <sub>4</sub> )	7.1:1:1:0	<b>f</b> (87)
4 <sup>[d]</sup>	<i>ent</i> - <b>f</b> (3-MeO-C <sub>6</sub> H <sub>4</sub> )	8.3:1:1:0	<i>ent</i> - <b>f</b> (82)
5	<b>g</b> (4-F-C <sub>6</sub> H <sub>4</sub> )	4.5:1:1:0	<b>g</b> (71)
6	<b>h</b> (4-Br-C <sub>6</sub> H <sub>4</sub> )	8.4:1:1:0	<b>h</b> (62)
7 <sup>[e]</sup>	<b>i</b> (2-furyl)	1.8:1.6:1:0	<b>i</b> (67)
8 <sup>[e]</sup>	<b>j</b> (CO <sub>2</sub> Et)	9.3:1.8:1:0	<b>j</b> (58)

<sup>[a]</sup> The reaction was carried out with imine **15** (1.0 equiv.), benzaldehyde (1.5 equivs.),  $\text{Rh}_2(\text{OAc})_4$  (2.0 mol %) and powdered 4 Å MS in  $\text{CH}_2\text{Cl}_2$  at 0°C with addition of ethyl diazoacetate (1.5 equivs.) over 10 h.

<sup>[b]</sup> Determined by  $^1\text{H}$  NMR spectroscopic analysis of the crude reaction mixture.

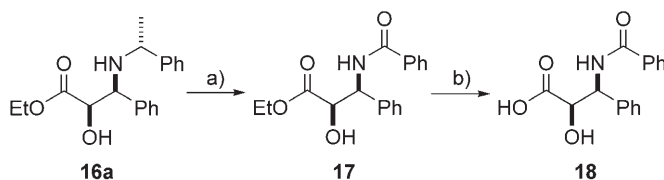
<sup>[c]</sup> Isolated yield (all isomers), major isomer separable from minor isomers with flash chromatography.

<sup>[d]</sup> Reaction performed using 2.0 g of (–)-imine.

<sup>[e]</sup> Reaction performed at –10°C.

ditions gave the corresponding cycloaddition products in low selectivity (entry 7).

The utility of the present methodology was exemplified with a short asymmetric synthesis of the paclitaxel side-chain **18**, which has previously been shown to be an important pharmacophore for the anti-tumor activity of the diterpene.<sup>[31]</sup> Compound **16a**, readily isolated from the two minor isomers, was subjected to catalytic hydrogenolysis followed by benzoylation to give amide **17** (77% yield, 2 steps, Scheme 5). Finally, hydrolysis of **17** using LiOH yielded the paclitaxel side chain **18** as a white solid in 4 steps and 53% overall yield. Analytical data of **18** were in all aspects identical to those previously reported.<sup>[4,18,32]</sup> This also

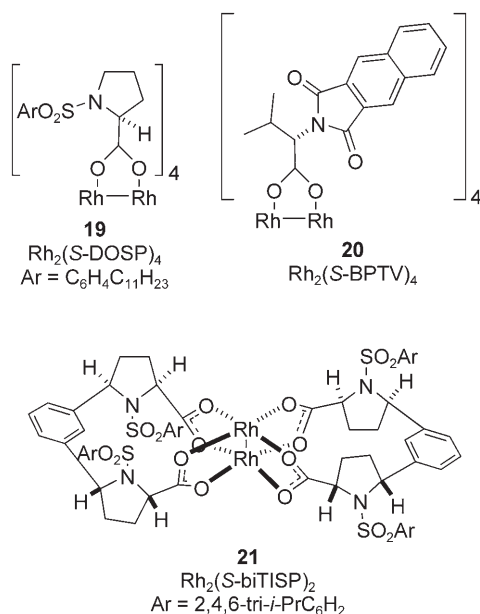


**Scheme 5.** Asymmetric synthesis of paclitaxel side-chain. *Reagents and conditions:* a) 1)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ , EtOH, 3 M HCl, room temperature; 2)  $\text{PhCOCl}$ ,  $\text{NaHCO}_3$ , EtOAc, 0°C (77% over 2 steps); b) LiOH·H<sub>2</sub>O, THF:MeOH:H<sub>2</sub>O (10:5:4), room temperature (89%).



proved the absolute stereochemistry of **16a**, obtained from (*R*)-imine **15a**, to be (2*R*, 3*S*).

Since it was noted that Lewis acids could have an impact on the outcome of these cycloadditions reactions using both achiral and chiral imines in combination with chiral Lewis acids were examined. Disappointingly, only low asymmetric inductions were obtained in these experiments (< 6% *ee*).<sup>[33]</sup>



**Figure 1.** Chiral Rh(II) catalysts.

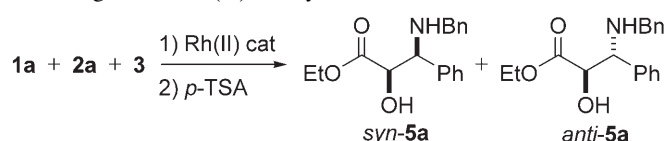
## Chiral Rh(II) Catalysts

In order to determine if the cycloaddition proceeds *via* the metal-free **6a** (Scheme 2) or the metal-associated ylide **6b** several Rh(II) catalysts having different ligands were screened. If **6b** is an intermediate it can be expected that different catalysts would give different stereochemical outcomes. Also, by employing chiral Rh(II) catalysts provides the opportunity to investigate the catalytic enantioselective 1,3-dipolar cycloaddition.

When exchanging Rh<sub>2</sub>(OAc)<sub>4</sub> for Rh<sub>2</sub>(pfb)<sub>4</sub> both yield and diastereoselectivity decreased (Table 1, entries 1 and 2). Employing Rh<sub>2</sub>(S-DOSP)<sub>4</sub> (**19**, Figure 1) under standard reaction conditions gave amino alcohol **5a** in good yield (62%) with excellent diastereoselectivity (*syn:anti* 94:6) and modest enantioselectivity (*er* 62:38) (Table 5, entry 1). Catalyst **19** has been reported to give best results in non-polar hydrocarbon solvents and when the reaction was performed in hexane the enantiomeric ratio was increased (82:18) albeit with decreased yield (17%, entry 2).<sup>[34]</sup> The same trend was observed when Et<sub>2</sub>O was used as solvent (entry 3). Unfortunately, both the Hashimoto catalyst<sup>[14b]</sup> [Rh<sub>2</sub>(S-BPTV)<sub>4</sub>, **20**] and the second generation Davies catalyst<sup>[35]</sup> [Rh<sub>2</sub>(S-biITISP)<sub>2</sub>, **21**], which have been reported to give excellent asymmetric induction in CH<sub>2</sub>Cl<sub>2</sub>, failed to give any improved results (entries 4 and 5).

Although it has been suggested that carbonyl ylides derived from EDA and benzaldehyde under Rh(II) catalysis involves the metal-free species **6a**, the present results clearly support involvement of metal-associated ylide **6b**.<sup>[14a]</sup> This is also the first example of an enantioselective intermolecular 1,3-dipolar cycloaddi-

**Table 5.** 1,3-Dipolar cycloadditions using chiral Rh(II) catalysts<sup>[a]</sup>



Entry	Catalyst	Solvent	Conditions <sup>[b]</sup> [°C/h]	<i>dr</i> <sup>[c]</sup> ( <i>syn:anti</i> )	<i>er</i> <sup>[d]</sup> ( <i>syn</i> )	Yield <sup>[e]</sup> <i>syn-5a</i> (%)
1	<b>19</b>	CH <sub>2</sub> Cl <sub>2</sub>	r.t./1	94:6	62:38	62
2	<b>19</b>	Hexane	r.t./1	71:29	82:18	17
3	<b>19</b>	Et <sub>2</sub> O	r.t./1	78:22	81:19	14
4	<b>20</b>	CH <sub>2</sub> Cl <sub>2</sub>	0/10	90:10	52:48	56
5	<b>21</b>	CH <sub>2</sub> Cl <sub>2</sub>	r.t./10	n.d.	n.d.	< 5 <sup>[f]</sup>

<sup>[a]</sup> The reaction was carried out with imine **1a** (1.0 equiv.), benzaldehyde (1.5 equivs.), chiral Rh(II) catalyst (2.0 mol %) and powdered 4 Å MS in CH<sub>2</sub>Cl<sub>2</sub> with addition of ethyl diazoacetate (1.5 equivs.).

<sup>[b]</sup> Reaction temperature and addition time.

<sup>[c]</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture.

<sup>[d]</sup> Determined by chiral HPLC (Chiracel OD-column).

<sup>[e]</sup> Isolated yield.

<sup>[f]</sup> **7** is the major product.

tion of carbonyl ylides to imines catalyzed by Rh(II) carboxylates.

## Conclusions

We have developed a three-component approach for the synthesis of *syn*- $\alpha$ -hydroxy- $\beta$ -amino esters based on a Rh(II)-catalyzed 1,3-dipolar cycloaddition of carbonyl ylides to imines. By using chiral  $\alpha$ -methylbenzylamines as dipolarophiles an asymmetric version of the cycloaddition was realized yielding enantiomerically pure *syn*- $\alpha$ -hydroxy- $\beta$ -amino esters, and this was applied in a short asymmetric synthesis of the paclitaxel side-chain. Furthermore, the use of chiral Rh(II) carboxylates affords the  $\beta$ -amino alcohols in modest enantioselectivity (*er* up to 82:18), which indicates that the reaction proceeds *via* a metal-associated carbonyl ylide.

## Experimental Section

For general experimental procedure, analytical data for compounds **5a**, **e–m** and NMR spectra for all new compounds, see Supporting Information.

### General Procedure for 1,3-Dipolar Cycloaddition of Carbonyl Ylides to Imines

To a solution of imine (0.256 mmol), benzaldehyde (39.0  $\mu$ L, 0.384 mmol), Rh<sub>2</sub>(OAc)<sub>4</sub> (2.3 mg, 5.12  $\mu$ mol) and powdered 4 Å MS (250 mg) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added diazoester (0.384 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) over 1 or 10 h at indicated temperature. The reaction mixture was stirred for an additional hour, filtered through a plug (pipette) of basic alumina (activity grade I), eluted with CH<sub>2</sub>Cl<sub>2</sub> (4–5 mL) and concentrated. The residue was dissolved in MeOH:H<sub>2</sub>O (4 mL, 95:5) and *p*-toluenesulfonic acid (0.340  $\mu$ L, 0.512 mmol, 1.5 M in MeOH) was added. The resultant mixture was stirred at room temperature for 2 h. The solvents were removed under reduced pressure and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NaHCO<sub>3</sub> solution. The aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated under vacuum. Flash chromatography of the residue gave the pure amino alcohol.

### (2*R*\*,3*S*\*)-(*R*)-Tetrahydro-4,4-dimethyl-2-oxofuran-3-yl 3-(Benzylamino)-2-hydroxy-3-phenylpropanoate (**14**)

The general procedure was followed using **1a** (53.6 mg, 0.256 mmol). Addition of diazoester **13** (76.1 mg, 0.384 mmol) over 10 h at 0 °C; *dr* 60:40; <sup>1</sup>H NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 2:1) of the residue gave **14** (81.0 mg, 82%, inseparable mixture of two diastereomers) as a pale yellow oil. Major isomer: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.29–7.07 (m, 10H), 5.27 (s, 1H), 4.33 (d, *J* = 4.6 Hz, 1H) ppm

3.94 (d, *J* = 4.6 Hz, 1H), 3.87 (m, 2H), 3.53 (d, *J* = 13.0 Hz, 1H), 3.38 (d, *J* = 13.0 Hz, 1H), (s, 3H), 0.77 (s, 3H). Minor isomer: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.29–7.07 (m, 10H), 5.23 (s, 1H), 4.31 (d, *J* = 4.2 Hz, 1H), 4.01 (d, *J* = 4.2 Hz, 1H), 3.87 (m, 2H), 3.59 (d, *J* = 12.8 Hz, 1H), 3.49 (d, *J* = 12.8 Hz, 1H), 1.05 (s, 3H), 0.86 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.3, 172.2, 171.9, 171.6, 139.6, 139.5, 139.3, 138.8, 128.7, 128.6, 128.33, 128.31, 128.28, 128.1, 128.0, 127.9, 127.84, 127.80, 127.03, 126.97, 76.23, 76.17, 76.1, 76.0, 75.9, 75.6, 74.8, 74.2, 64.2, 64.1, 51.3, 50.9, 40.2, 40.1, 22.85, 22.83, 22.6, 19.6, 19.5; IR (film):  $\nu_{\max}$  = 3448 (br), 2966, 1786, 1757, 1111 cm<sup>−1</sup>; HR-MS (FAB+): *m/z* = 384.1810, calcd. for C<sub>22</sub>H<sub>26</sub>NO<sub>5</sub> (M+H): 384.1811.

### (2*R*,3*S*)-Ethyl 3-(Benzylamino)-2-hydroxy-3-phenylpropanoate (**5a**)

To a solution of **14** (32.0 mg, 0.083 mmol, 60:40 mixture of diastereomers) and dry EtOH (97  $\mu$ L, 1.67 mmol) in PhMe (2 mL) was added Ti(O-*i*-Pr)<sub>4</sub> (7.5  $\mu$ L, 0.025 mmol) under N<sub>2</sub>. The reaction mixture was heated to reflux over night and quenched with 1 M HCl (1 mL). Extrelut<sup>®</sup> work-up followed by flash chromatography (heptane:EtOAc, 4:1) of the residue gave **5** (15.0 mg, 60%) as a white solid (*er* 60:40, Chiracel OD column, 15% isopropanol-hexanes, 0.5 mL min<sup>−1</sup>; *t*<sub>R(minor)</sub> = 11.2 min, *t*<sub>R(major)</sub> = 15.6 min); mp 76–77 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.38–7.23 (m, 10H), 4.23 (d, *J* = 4.0 Hz, 1H), 4.21–4.11 (m, 2H), 3.95 (d, *J* = 4.0 Hz, 1H), 3.76 (d, *J*<sub>AB</sub> = 13.3 Hz, 1H), 3.50 (d, *J*<sub>AB</sub> = 13.3 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 173.5, 140.0, 139.6, 128.5, 128.3, 128.2, 127.8, 127.0, 74.9, 63.6, 61.7, 50.7, 14.0; IR (film):  $\nu_{\max}$  = 3467 (br), 2981, 1734, 1100 cm<sup>−1</sup>; HR-MS (FAB+): *m/z* = 300.1601, calcd for C<sub>18</sub>H<sub>22</sub>NO<sub>3</sub> (M+H): 300.1600.

### (2*R*,3*S*)-Ethyl 3-[(*S*)-1-Phenylethylamino]-2-hydroxy-3-phenylpropanoate (**16a**)

The general procedure was followed using **15a** (53.6 mg, 0.256 mmol). Addition of ethyl diazoacetate over 10 h at 0 °C; *dr* 8:1:1:0, <sup>1</sup>H NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc 5:1) of the residue gave **16a** (49.0 mg, 61%) as a white solid and an inseparable mixture of two minor diastereomers (12.6 mg, 16%) as a clear oil. Major isomer: mp 84–86 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup>: 11.3 (c 0.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.32–7.12 (m, 10H), 4.23–4.15 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.11 (d, *J* = 3.2 Hz, 1H), 4.07–3.99 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.66 (d, *J* = 3.2 Hz, 1H), 3.46 (q, *J* = 6.6 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 173.5, 145.1, 140.1, 128.4, 128.2, 127.7, 127.5, 126.9, 74.9, 61.8, 61.5, 54.4, 25.2, 13.9; IR (film):  $\nu_{\max}$  = 3421 (br), 2975, 1730, 1451, 1104 cm<sup>−1</sup>; HR-MS (FAB+): *m/z* = 314.1754, calcd. for C<sub>19</sub>H<sub>24</sub>NO<sub>3</sub> (M+H): 314.1756.

### (2*R*,3*S*)-Ethyl 3-[(*R*)-1-Phenylethylamino]-2-hydroxy-3-(4-methoxyphenyl)propanoate (**16e**)

The general procedure was followed using **15e** (61.3 mg, 0.256 mmol). Addition of ethyl diazoacetate over 10 h at 0 °C; *dr* 5.4:1:1:0, <sup>1</sup>H NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 6:1→2:1) of the residue gave **16e** (51.1 mg, 58%) as a pale

yellow oil and an inseparable mixture of two minor diastereomers (24.3 mg, 28%) as a pale yellow oil. Major isomer:  $[\alpha]_D^{20}$ : 103.1 (c 1.1,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.32 (m, 7H), 6.98 (m, 2H), 4.30 (qd,  $J$  = 10.7, 7.2 Hz, 1H), 4.20 (d,  $J$  = 3.4 Hz, 1H), 4.15 (qd,  $J$  = 10.7, 7.2 Hz, 1H), 3.90 (s, 3H), 3.73 (d,  $J$  = 3.4 Hz, 1H), 3.57 (q,  $J$  = 6.6 Hz, 1H), 1.34 (d,  $J$  = 6.6 Hz, 3H), 1.23 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.5, 159.0, 145.2, 132.0, 128.7, 128.2, 126.92, 126.87, 113.8, 75.0, 61.7, 60.8, 55.2, 54.3, 25.1, 13.9; IR (film):  $\nu_{\text{max}}$  = 3487 (br), 2962, 1732, 1248, 1109  $\text{cm}^{-1}$ ; HR-MS (FAB+):  $m/z$  = 344.1875, calcd. for  $\text{C}_{20}\text{H}_{26}\text{NO}_4$  (M+H): 344.1862.

**(2R,3S)-Ethyl 3-[(R)-1-Phenylethylamino]-2-hydroxy-3-(3-methoxyphenyl)propanoate (16f)**

The general procedure was followed using **15f** (61.3 mg, 0.256 mmol). Addition of ethyl diazoacetate over 10 h at 0°C; *dr* 7.1:1.1:0;  $^1\text{H}$  NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 6:1→2:1) of the residue gave **16f** (59.3 mg, 67%) as a clear oil and an inseparable mixture of two minor diastereomers (17.4 mg, 20%) as a clear oil. Major isomer:  $[\alpha]_D^{20}$ : 110.8 (c 1.2,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.30 (m, 4H), 7.22 (m, 2H), 6.88 (m, 3H), 4.27 (qd,  $J$  = 10.7, 7.2 Hz, 1H), 4.19 (d,  $J$  = 3.2 Hz, 1H), 4.11 (qd,  $J$  = 10.7, 7.2 Hz, 1H), 3.84 (s, 3H), 3.71 (d,  $J$  = 3.2 Hz, 1H), 3.56 (q,  $J$  = 6.6 Hz, 1H), 1.30 (d,  $J$  = 6.6 Hz, 3H), 1.19 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.5, 159.8, 145.2, 141.8, 129.4, 128.2, 127.0, 126.9, 120.0, 113.4, 112.7, 74.9, 61.8, 61.4, 55.2, 54.4, 25.2, 13.9; IR (film):  $\nu_{\text{max}}$  = 3473 (br), 2978, 1736, 1254, 1107  $\text{cm}^{-1}$ ; HR-MS (FAB+):  $m/z$  = 344.1860, calcd. for  $\text{C}_{20}\text{H}_{26}\text{NO}_4$  (M+H): 344.1862.

**(2S,3R)-Ethyl 3-[(S)-1-Phenylethylamino]-2-hydroxy-3-(3-methoxyphenyl)propanoate (ent-16f)**

The general procedure was followed using *ent*-**15f** (2.0 g, 8.36 mmol). Addition of ethyl diazoacetate over 10 h at 0°C; *dr* 8.3:1.1:0;  $^1\text{H}$  NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 6:1→2:1) of the residue gave *ent*-**16f** (1.840 g, 64%) as a pale yellow oil and an inseparable mixture of two minor diastereomers (0.506 g, 18%) as a pale yellow oil. Major isomer:  $[\alpha]_D^{20}$ : −109.2 (c 1.3,  $\text{CHCl}_3$ ).

**(2R,3S)-Ethyl 3-[(R)-1-Phenylethylamino]-3-(4-fluorophenyl)-2-hydroxypropanoate (16g)**

The general procedure was followed using **15g** (58.2 mg, 0.256 mmol). Addition of ethyl diazoacetate over 10 h at 0°C; *dr* 4.5:1.1:0;  $^1\text{H}$  NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 6:1→4:1) of the residue gave **16g** (41.0 mg, 48%) as a clear oil and an inseparable mixture of two minor diastereomers (19.6 mg, 23%) as a clear oil. Major isomer:  $[\alpha]_D^{20}$ : 93.5 (c 2.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.29 (m, 5H), 7.19 (m, 2H), 7.07 (m, 2H), 4.27 (qd,  $J$  = 10.7, 7.1 Hz, 1H), 4.14 (d,  $J$  = 3.3 Hz, 1H), 4.12 (qd,  $J$  = 10.7, 7.1 Hz, 1H), 3.71 (d,  $J$  = 3.3 Hz, 1H), 3.48 (q,  $J$  = 6.6 Hz, 1H), 1.29 (d,  $J$  = 6.6 Hz, 3H), 1.19 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.4, 163.2, 161.3, 144.9, 135.8, 135.7, 129.32, 129.26, 128.3, 127.0, 126.9, 115.3, 115.2, 74.8, 61.9, 60.7, 54.3,

25.2, 13.9; IR (film)  $\nu_{\text{max}}$  = 3496 (br), 2980, 1736, 1221, 1107  $\text{cm}^{-1}$ ; HR-MS (FAB+):  $m/z$  = 332.1664, calcd. for  $\text{C}_{19}\text{H}_{23}\text{FNO}_3$  (M+H) 332.1662.

**(2R,3S)-Ethyl 3-[(R)-1-phenylethylamino]-3-(4-bromophenyl)-2-hydroxypropanoate (16h)**

The general procedure was followed using **15h** (73.8 mg, 0.256 mmol). Addition of ethyl diazoacetate over 10 h at 0°C; *dr* 8.4:1.1:0;  $^1\text{H}$  NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 6:1→4:1) of the residue gave **16h** (51.1 mg, 51%) as a clear oil and an inseparable mixture of two minor diastereomers (11.0 mg, 11%) as a clear oil. Major isomer:  $[\alpha]_D^{20}$ : 334.7 (c 1.3,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.51 (m, 2H), 7.28 (m, 3H), 7.18 (m, 4H), 4.28 (qd,  $J$  = 10.7, 7.2 Hz, 1H), 4.14 (d,  $J$  = 3.2 Hz, 1H), 4.13 (qd,  $J$  = 10.7, 7.2 Hz, 1H), 3.70 (d,  $J$  = 3.2 Hz, 1H), 3.48 (q,  $J$  = 6.6 Hz, 1H), 1.29 (d,  $J$  = 6.6 Hz, 3H), 1.20 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.3, 144.8, 139.1, 131.5, 129.5, 128.2, 127.0, 126.9, 121.4, 74.6, 62.0, 60.8, 54.4, 25.1, 13.9; IR (film):  $\nu_{\text{max}}$  = 3487 (br), 2977, 1736, 1252, 1215, 1107  $\text{cm}^{-1}$ ; HR-MS (FAB+):  $m/z$  = 392.0876, calcd. for  $\text{C}_{19}\text{H}_{23}\text{BrNO}_3$  (M+H) 392.0861.

**(2R,3R)-Ethyl 3-[(R)-1-Phenylethylamino]-3-(furan-2-yl)-2-hydroxypropanoate (16i)**

The general procedure was followed using **15i** (102.0 mg, 0.512 mmol). Addition of ethyl diazoacetate over 10 h at −10°C; *dr* 1.8:1.6:1:0;  $^1\text{H}$  NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 6:1→4:1) of the residue gave **16i** (43.6 mg, 28%) as a clear oil and an inseparable mixture of two minor diastereomers (60.9 mg, 39%) as a clear oil. Major isomer:  $[\alpha]_D^{20}$ : 127.2 (c 1.2,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.42 (dd,  $J$  = 1.7, 0.7 Hz, 1H), 7.27 (m, 5H), 6.36 (dd,  $J$  = 3.2, 1.8 Hz, 1H), 6.21 (d,  $J$  = 3.1 Hz, 1H), 4.29 (d,  $J$  = 3.1 Hz, 1H), 4.24 (qd,  $J$  = 10.6, 7.1 Hz, 1H), 4.05 (qd,  $J$  = 10.7, 7.2 Hz, 1H), 3.81 (d,  $J$  = 3.1 Hz, 1H), 3.65 (q,  $J$  = 6.6 Hz, 1H), 1.28 (d,  $J$  = 6.6 Hz, 3H), 1.15 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.0, 153.9, 144.9, 142.1, 128.2, 127.1, 127.0, 110.1, 107.6, 73.3, 61.9, 55.6, 55.0, 25.1, 13.9; IR (film):  $\nu_{\text{max}}$  = 3483 (br), 2978, 1738, 1105  $\text{cm}^{-1}$ ; HR-MS (FAB+):  $m/z$  = 304.1560, calcd. for  $\text{C}_{17}\text{H}_{22}\text{NO}_4$  (M+H): 304.1549.

**(2R,3R)-Diethyl 2-[(R)-1-Phenylethylamino]-3-hydroxysuccinate (16j)**

The general procedure was followed using **15j** (52.5 mg, 0.256 mmol). Addition of ethyl diazoacetate over 10 h at −10°C; *dr* 9.3:1.8:1:0;  $^1\text{H}$  NMR spectroscopic analysis on the crude product. Flash chromatography (heptane:EtOAc, 6:1→4:1) of the residue gave **16j** (39.0 mg, 49%) as a clear oil and an inseparable mixture of two minor diastereomers (7.1 mg, 9%) as a clear oil. Major isomer:  $[\alpha]_D^{20}$ : 74.0 (c 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.28 (m, 5H), 4.45 (dd,  $J$  = 4.4, 2.0 Hz, 1H), 4.28 (m, 3H), 3.97 (qd,  $J$  = 10.6, 7.2 Hz, 1H), 3.78 (q,  $J$  = 6.5 Hz, 1H), 3.44 (d,  $J$  = 2.1 Hz, 1H), 3.22 (d,  $J$  = 5.2 Hz, 1H), 2.26 (br s, 1H), 1.36 (d,  $J$  = 6.5 Hz, 3H), 1.33 (t,  $J$  = 7.1 Hz, 3H), 1.13 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 172.4, 172.3, 144.9, 128.2, 127.1, 72.2, 62.1, 61.3, 60.8, 56.6, 25.1, 14.2, 13.8; IR (film):



$\nu_{\max}$  = 3483 (br), 2980, 1741, 1223, 1105  $\text{cm}^{-1}$ ; HR-MS (FAB+):  $m/z$  = 310.1648, calcd. for  $\text{C}_{16}\text{H}_{24}\text{NO}_5$  (M+H): 310.1654.

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