Catalytic Enantioselective Allylic Amination of Olefins for the Synthesis of *ent*-Sitagliptin

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Abstract: The presence of nitrogen atoms in most chiral pharmaceutical drugs has motivated the development of numerous strategies for the synthesis of enantiomerically enriched amines. Current methods are based on multistep transformations of functionalized allylic electrophiles to form chiral allylic amines. The enantioselective allylic amination of nonactivated olefins would represent a more direct and more attractive strategy. We report the enantioselective synthesis of *ent*-sitagliptin through an allylic amination of a nonactivated terminal olefin.

Key words: asymmetric catalysis, aminations, drugs, rearrangements, palladium

Nitrogen atoms are present in more than 80% of pharmaceutical drugs approved by the U.S. Food and Drug Administration (FDA).[1,2] The presence of nitrogen atoms in small molecules leads to desirable medicinal properties, including improved solubility under physiological conditions, favorable polar surfaces, and hydrogen-bonding interactions with amino acid residues. As a result, many powerful chemical methods have been developed for the incorporation of nitrogen atoms into small molecules, with profound effects on the discovery of new drugs.[3]

Chiral amines represent an important subclass of medicinally relevant nitrogen-containing molecules.[4] For example, sitagliptin (**1**) is an FDA-approved inhibitor of dipeptidyl peptidase-4 for the treatment of Type II diabetes (Scheme 1).[5,6] Several elegant enantioselective methods have been developed for the synthesis of chiral amines **4** from allylic alcohols and other allylic electrophiles, such as allylic halides **3**.[7]

We were interested in developing an alternative approach for the preparation of chiral amines **4** by direct conversion of nonfunctionalized olefins **2** through an allylic amination in the presence of a chiral catalyst.[8] Unsaturated hydrocarbons such as **2** are ideal substrates for chemical synthesis because they are inexpensive and abundant components of petrochemical feedstocks.[9] However, olefins are also challenging substrates for asymmetric catalysis, because it is difficult to achieve selective transformation of a single C–H bond into a C–N bond in the presence of several sterically and electronically similar C–H bonds.

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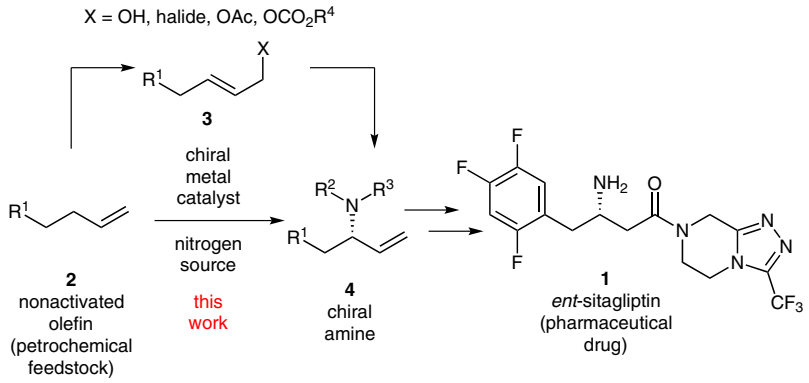
Uttam K. Tambar (middle) moved from India to the USA when he was four years old. He received his A.B. degree from Harvard University in 2000 and his Ph.D. from the California Institute of Technology in 2006, under the supervision of Professor Brian Stoltz. After completing an NIH Postdoctoral Fellowship at Columbia University with Professor James Leighton in 2009, Uttam began his independent research career at UT Southwestern Medical Center in Dallas. He is currently an assistant professor in the Biochemistry Department and a W. W. Caruth, Jr. Scholar in Biomedical Research. His research interests include asymmetric catalysis, natural product synthesis, and medicinal chemistry.

Hongli Bao (right) received her B.S. degree in chemistry from the University of Science and Technology of China in 2002. She obtained her Ph.D. through the joint program of the Shanghai Institute of Organic Chemistry and the University of Science & Technology of China in 2008 under the supervision of Professor Kuiling Ding and Professor Tianpa You. She joined the Tambar group in 2009, and she is interested in developing metal-catalyzed enantioselective [2,3]-rearrangements. Hongli is a recipient of the UT Southwestern Chilton Postdoctoral Fellowship in Biochemistry.

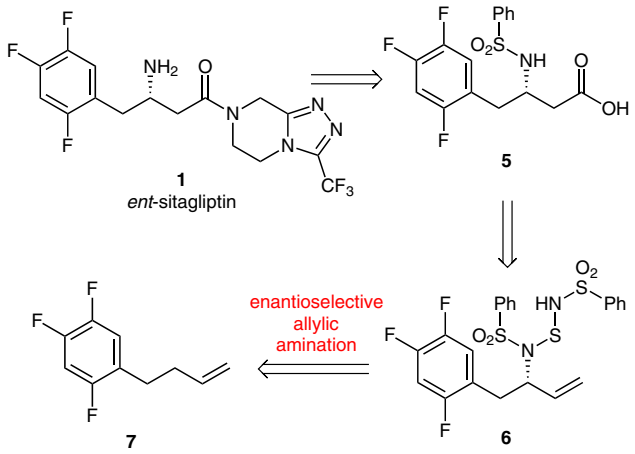
Liela Bayeh (left) received her B.S. degree in Biochemistry from Baylor University in 2011 and then moved on to UT Southwestern Medical Center in Dallas to complete her Ph.D. studies. Since joining the Tambar laboratory in 2012, her research has focused primarily on asymmetric catalysis and medicinal chemistry.

We recently reported a palladium-catalyzed enantioselective allylic amination of nonactivated terminal olefins through an ene reaction/[2,3]-rearrangement.[10] Here, we describe the application of this approach to the enantioselective synthesis of *ent*-sitagliptin (**1**).

Several elegant approaches to sitagliptin have been reported in the literature.[6] Most notably, researchers at Merck developed multiple enantioselective routes to this compound.[6a–d,6g] In our retrosynthetic analysis of *ent*-sitagliptin (Scheme 2), we surmised that the target molecule **1** might be obtained from β-amino acid **5**. This intermediate might, in turn, be generated from the allylic amine derivative **6** through a series of functional-group interconversions. Enantiomerically enriched allylic amine **6** is a suitable retron for our recently developed catalytic enantioselective allylic amination of nonactivated olefins. The analysis therefore suggested that 1-but-3-en-1-yl-



Scheme 1 Strategies for the conversion of nonactivated olefins into chiral allylic amines



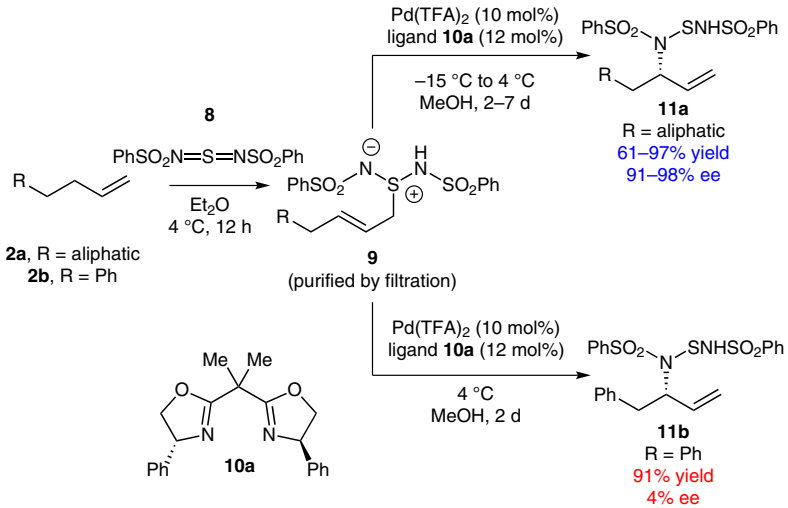
Scheme 2 Retrosynthetic analysis of sitagliptin

2,4,5-trifluorobenzene (**7**) would be a suitable starting point for our synthetic efforts.

In an initial report, we described a catalytic enantioselective intermolecular allylic amination of nonactivated terminal olefins that are substituted with aliphatic substituents (**2a** → **11a**, Scheme 3).[10] This transformation proceeds through a two-step ene reaction/[2,3]-rearrangement, the discovery of which was inspired by the seminal reports of Sharpless, Kresze, and Katz and their respective co-workers on the conversion of olefins into racemic allylic amines.[11] In the first step, a nonactivated olefin **2a** reacts with sulfurdiimide reagent **8** through a hetero-ene reaction. The resulting zwitterion **9a** is subjected to a palladium-catalyzed enantioselective [2,3]-rearrangement to give the desired allylic amine **11a**.

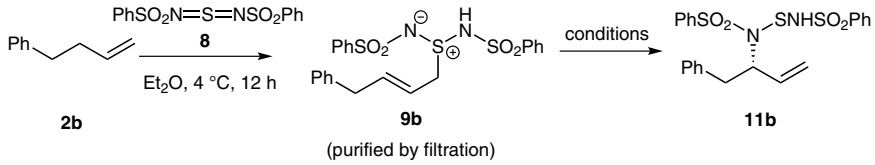
As a model system for our first step in the synthesis of *ent*-sitagliptin (**7** → **6**, Scheme 2), we selected but-3-en-1-yl-benzene (**2b**), which lacked the three fluoride substituents in the aromatic ring of olefin **7** (Scheme 3). We expected that our carefully optimized conditions for the palladium-catalyzed generation of allylic amines **11a** with aliphatic substitution at the homoallylic position would also be suitable for the conversion of aryl alkene **2b** into the allylic amine **11b** with aromatic substitution at the homoallylic position. To our dismay, however, in the presence of 10 mol% palladium(II) trifluoroacetate and 12 mol% of ligand **10a**, the allylic amine **11b** was generated in only 4% enantiomeric excess (Table 1, entry 2).

Although we still do not known why terminal olefins with aromatic substitution in the homoallylic position do not behave well under our previously optimized conditions,

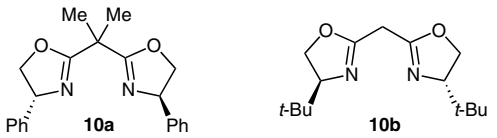


Scheme 3 Allylic aminations of alkene substrates

Table 1 Optimization of Enantioselective Allylic Amination



Entry	Metal catalyst (10 mol%)	Ligand (mol%)	Solvent (0.13 M)	Temp (°C)	Time (d)	Yield[a]	ee (%)
1	–	–	–	4	0.5	< 5	–
2	$Pd(TFA)_2$	**10a** (12)	CH_2Cl_2	4	2	91	4
3	$Pd(OAc)_2$	**10a** (12)	MeOH	4	0.5	71	19
4	$Pd(OAc)_2$	**10b** (12)	CH_2Cl_2	4	0.5	75	79
5	$Pd_2(dba)_3$	**10b** (12)	CH_2Cl_2	4	2	60	0
6	$PdCl_2(MeCN)_2$	**10b** (12)	CH_2Cl_2	4	2	63	6
7	$Pd(acac)_2$	**10b** (12)	CH_2Cl_2	4	2	73	0
8	$Pd(TFA)_2$	**10b** (12)	CH_2Cl_2	4	2	80	85
9	$Pd(TFA)_2$	**10b** (12)	DCE	4	2	94	91
10	$Pd(TFA)_2$	**10b** (20)	DCE	–15	7	94	93



[a] Isolated yield for two steps.

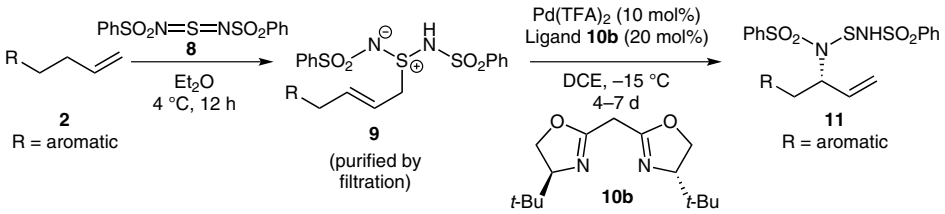
we decided to reoptimize all the conditions for the palladium-catalyzed [2,3]-rearrangement step with the model substrate but-3-en-1-ylbenzene (**2b**) (Table 1). We confirmed that zwitterion **9b** did not undergo a thermal [2,3]-rearrangement in the absence of a palladium catalyst at 4 °C (Table 1, entry 1). As discussed above, treatment of zwitterion **9b** with ligand **10a** under our previously optimized conditions resulted in an almost racemic product (entry 2). After surveying other bisoxazoline and bisoxazolinyl-pyridine ligands with palladium(II) acetate, we found that bisoxazoline **10b** was a more effective ligand than bisoxazoline **10a** (entries 3 and 4), giving the desired product in 75% yield and 79% ee (entry 4).[12] We also examined a series of palladium sources (entries 5–8), among which palladium(II) trifluoroacetate proved to be the most promising (entry 8). We were now able to isolate the desired product in 80% yield and 85% ee. By screening several solvents,[12] we identified 1,2-dichloroethane as the optimal medium for the reaction (entry 9). Finally, by lowering the reaction temperature to –15 °C and increasing the loading of ligand **10b** to 20 mol%, we generated allylic amination product **11b** in 94% isolated yield (two steps) and 93% ee (entry 10).

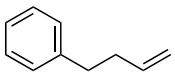
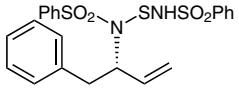
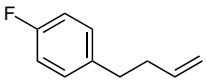
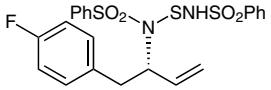
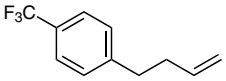
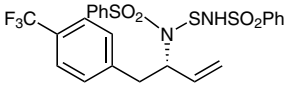
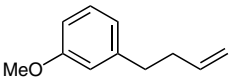
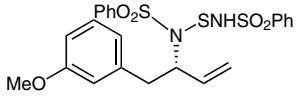
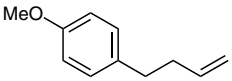
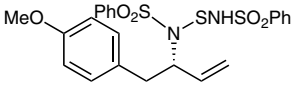
Having identified the optimal conditions, we then converted a series of 4-arylbut-1-ene substrates **2** into the corresponding enantiomerically enriched allylic amine derivatives **11** (Table 2).[13] This reaction tolerated both electron-withdrawing and electron-donating substituents. In all cases, the allylic amination products **11** were isolated in synthetically useful yields and enantiomeric excesses.

Next, we used our new reaction conditions in an enantioselective allylic amination of 1-but-3-en-1-yl-2,4,5-trifluorobenzene (**7**) as a step in our synthesis of *ent*-sitagliptin (Scheme 4). To our delight, aryl alkene **7** was smoothly converted into the desired allylic amine derivative **6** by a hetero-ene reaction followed by a palladium-catalyzed enantioselective [2,3]-rearrangement. Treatment of the resulting allylic amination product **6** with methanolic potassium carbonate gave the allylic sulfonamide **12** in 78% yield (three steps) and 93% ee. Hydroboration and extensive oxidation of olefin **12** gave the β-amino acid **5**. Coupling of amino acid **5** with amine **13**, and subsequent deprotection of the sulfonamide gave *ent*-sitagliptin (**1**).

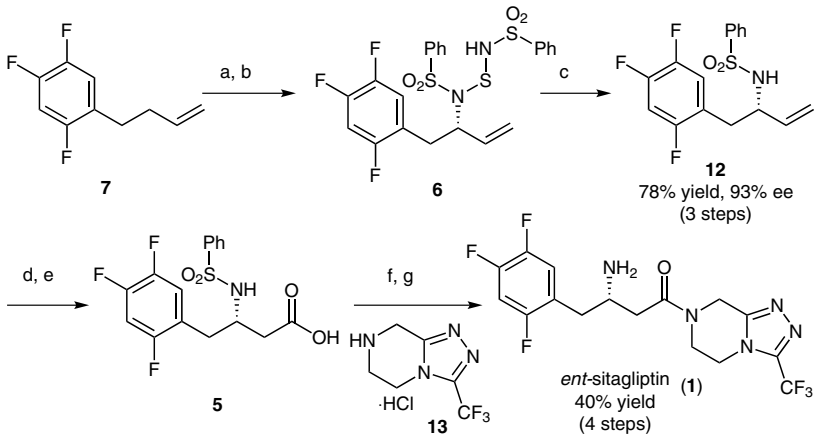
In conclusion, our synthesis of *ent*-sitagliptin highlights the potential utility of enantioselective allylic amination as an economically efficient and environmentally benign alternative for the production of pharmaceutical drugs. We expect that this method will be useful for the synthesis of other nitrogen-containing pharmaceutical agents from inexpensive and abundant nonactivated olefins.

Table 2 Substrate Scope of Enantioselective Allylic Amination



Entry	Olefin	Product	Yield[a]	ee (%)
1			94	93
2			89	90
3			79	90
4			83	95
5			84	81

[a] Isolated yield for two steps.



Scheme 4 Enantioselective synthesis of *ent*-sitagliptin. *Reaction conditions*: (a) **8**, Et_2O, 4 °C, 12 h; (b) $Pd(TFA)_2$ (10 mol%), ligand **10h** (20 mol%), DCE, –15°C, 7 d; (c) K_2CO_3, MeOH, H_2O, 16 h; (d) 9-BBN, THF, then aq NaOH, H_2O_2; (e) CrO_3, H_5IO_6, MeCN, 0 °C; (f) **13**, 1*H*-1,2,3-benzotriazol-1-ol, EDC, DIPEA, DMF; (g) MsOH, TFA, PhSMe, 40 °C.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) For a more complete account of the optimization of the reaction parameters, see Table S1 in the Supporting Information.

(13) ***N*-[(1*S*)-1-Benzylprop-2-en-1-yl]-*N*-{[(phenylsulfonyl)amino]sulfanyl}benzenesulfonamide (11b); Typical Procedure**
A 0.5 M solution of diimide **8** (685 mg, 2 mmol) in Et_2O (4 mL) was cooled to 0 °C and treated with but-3-en-1-ylbenzene (6 mmol, 3 equiv), and the mixture was stirred at 4 °C for 12 h. The ene adduct **9**, which formed as a white precipitate, was purified by vacuum filtration at r.t., washed with Et_2O (20–40 mL), and dried under vacuum. The ene adduct **9** was then suspended in DCE (5 mL) and the suspension was cooled to –20 °C then treated with a Pd–ligand complex in DCE (10 mL). The Pd–ligand complex was prepared by mixing $Pd(TFA)_2$ (10 mol%) and ligand **10b** (20 mol%) in DCE (10 mL), and stirring for 30 min at 50 °C. The ene adduct-containing mixture was warmed to –15 °C and stirred for 7 d. Purification by flash chromatography [hexanes–EtOAc (20:1 to 5:1)] gave a clear oil; yield: 887 mg (94%, two steps); $[\alpha]_D^{23}$ = +93.0 (*c* 1.0, CH_2Cl_2). The enantiomeric excess of the product was determined to be 93% by comparison with a sample of the racemate. IR (thin film): 3234, 1447, 1352, 1165, 1088, 806 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 7.90 (d, *J* = 7.5 Hz, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 4 H), 7.37 (m, 2 H), 7.18–7.10 (m, 6 H), 6.95 (s, 1 H), 6.10 (br s, 1 H), 5.07 (m, 2 H), 4.80 (m, 1 H), 3.23 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ = 140.9, 139.6, 137.8, 133.4, 133.3, 129.6, 129.4, 129.1, 28.6, 127.9, 127.3, 126.7, 118.9, 68.2, 39.9. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $[C_{22}H_{22}N_2O_4S_3Na]^+$: 497.0634; found: 497.0645.

