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Iridium(I)-Catalyzed Stereospecific Decarboxylative Allylic Amidation of Chiral Branched Benzyl Allyl Imidodicarboxylates

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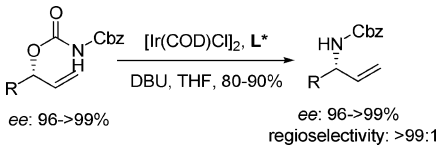
ABSTRACT



Ir(I)-catalyzed decarboxylative allylic amidation of chiral branched benzyl allyl imidodicarboxylates has been shown to proceed with complete retention of enantiomeric purity and configuration. The transformation is stereospecific and appears to be quite general, accommodating a wide range of R groups.

We recently reported the Ir(I)-catalyzed regio- and enantioselective decarboxylative allylic amidation of benzyl allyl imidodicarboxylates **1**, which could directly give rise to the formation of *N*-Cbz-protected chiral allylic amines **2** (Figure 1).[1,2] The reaction was effected by $[Ir(COD)Cl]_2$, a chiral phosphoramidite ligand **L***, DBU, and proton sponge (PS) in THF and appeared to show some generality, accommodating a variety of R groups.

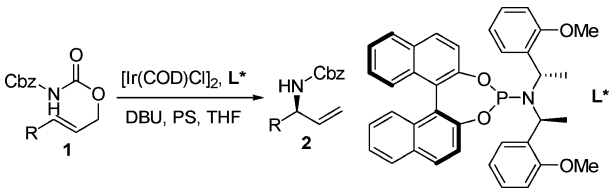
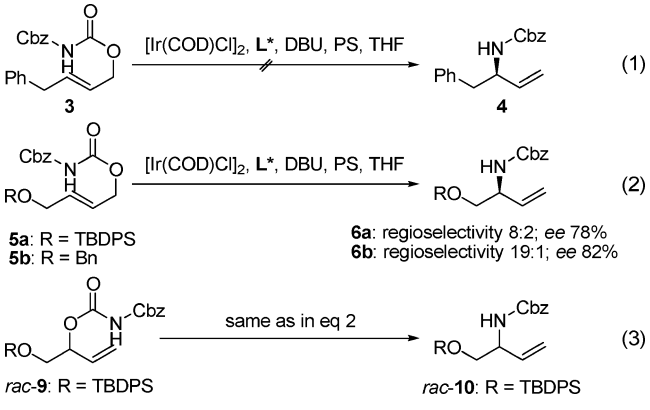


Figure 1. Ir(I)-catalyzed decarboxylative allylic amidation.

However, during the course of further investigation of the scope and limitations of the reaction, it was found that some allylic substrates did not work well under the determined reaction conditions. For example, upon the decarboxylative allylic amidation, benzyl 4-phenylbut-2-enyl imidodicarboxylate (**3**) could not furnish the chiral branched allylic amidation product **4** (due to a competing elimination reaction to form 1-phenyl-1,3-butadiene) (eq 1), and the conversion of the allylic substrates **5** to **6** suffered from modest regio- and enantioselectivities (eq 2).



Herein, we disclose the Ir(I)-catalyzed stereospecific decarboxylative allylic amidation of **7** to **8** (Figure 2), which

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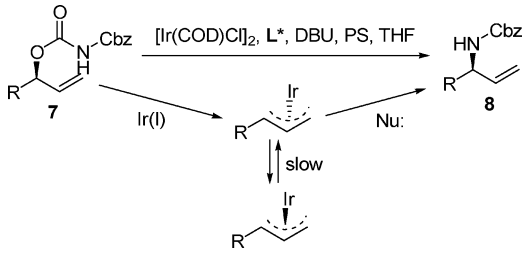

Figure 2. Ir(I)-catalyzed stereospecific decarboxylative allylic amidation reaction of optically enriched branched benzyl allyl imidodicarboxylates.

can provide not only **4** and **6** but also the decarboxylative allylic amidation products that could not be easily accessed by the Ir(I)-catalyzed regio- and enantioselective decarboxylative allylic amidation of **1**.

At the outset, racemic benzyl 1-(*tert*-butyldiphenylsilyloxy)-but-3-ene-2-yl imidodicarboxylate (*rac*-**9**) was prepared (see below), and subjected to the reaction conditions involving $[Ir(COD)Cl]_2$, a chiral phosphoramidite ligand **L***, DBU, and proton sponge (PS) in THF. Racemic 2-*N*-benzyloxycarbonylamino-1-(*tert*-butyldiphenylsilyloxy)-but-3-ene (*rac*-**10**) was obtained in excellent reaction yield and regioselectivity (eq 3). Further experiments revealed that PS was not required for the reaction. These results indicate that the optically enriched chiral benzyl allyl imidodicarboxylates **7** should lead to the corresponding optically enriched allylic amidation products **8** with complete retention of configuration under the above conditions, because (1) Ir(I)-catalyzed allylic alkylation followed a double inversion mechanism through the Ir-π-allyl intermediates, and the interconversion between the Ir-π-allyl intermediates was slow relative to the other catalytic steps (see Figure 2)[3,4] and (2) the branched allylic acetates and carbonates were better (with respect to regioselectivity) and faster substrates than their linear counterparts in the Ir(I)-catalyzed allylic substitution reactions.[3,5]

With such a premise, a variety of optically enriched benzyl allyl imidodicarboxylates **7** and their enantiomers *ent*-**7** were prepared from the corresponding aldehydes **11** in three or four steps according to the general procedure shown in Scheme 1.[1,3a] **7** and *ent*-**7** were obtained by the enzymatic resolution of the racemic allylic alcohols **12** followed by the

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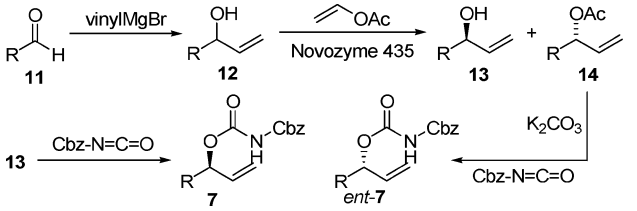
Scheme 1. Preparation of Optically Enriched Branched Allyl Benzyl Imidodicarboxylates



conversion of the resulting optically enriched allylic alcohols **13** and their acetates **14** to the corresponding benzyl imidodicarboxylates **7** and *ent*-**7**, respectively (see the Supporting Information [SI] for details).

The Ir(I)-catalyzed decarboxylative allylic amidation reactions of **7** and *ent*-**7** were conducted under the determined conditions involving $[Ir(COD)Cl]_2$, a chiral phosphoramidite ligand **L***, and DBU in THF,[6] and the results are depicted in Table 1. The stereospecific decarboxylative allylic amidation appears to be quite general, accommodating a wide range of R groups such as aryl (entries 1 and 2), benzyl (entry 3), oxygen atom functionalized at the α-carbon (entries 4−6), oxygen atom functionalized at the β-carbon (entry 7), cyclohexyl (entry 8), and cyclohexenyl (entries 9 and 10).

Except for entries 1 and 2, all other allylic amidation products in entries 3−10 either were not possible to obtain or were obtained with modest regio- and enantioselectivities from the corresponding decarboxylative allylic amidation reactions of **1**. The data from Table 1 also show that the optical purities of the allylic substrates were completely translated into those of the allylic amidation products with retention of configuration, as expected from the double inversion mechanism and the slow interconversion between the Ir-π-allyl intermediates. The presence of an additional adjacent chiral center did not interfere with chirality transfer (entries 9 and 10). Such complete chirality transfer in the Ir(I)-catalyzed decarboxylative allylic amidation of **7** and *ent*-**7** is in sharp contrast to the corresponding Ir(I)-catalyzed stereospecific allylic alkylation, where considerable erosion in chirality transfer took place.[3b]

To ascertain the absolute stereochemistry at the allylic carbon of the amidation products and to determine the ee of the amidation product in entry 3, the amidationproduct **15** was transformed to *N*-Cbz protected L-phenylalanine by the oxidative cleavage of the terminal double bond.[7] The optical rotation of the resulting product matched that in the literature (Scheme 2).[8]

Scheme 2. Synthesis of *N*-Cbz-Protected L-Phenylalanine

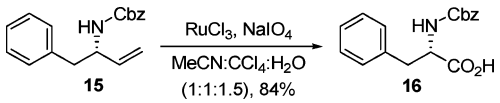
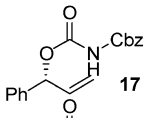
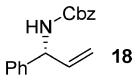
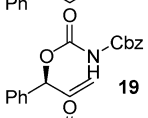
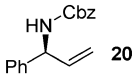
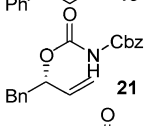
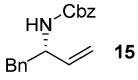
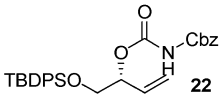
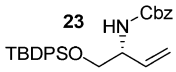
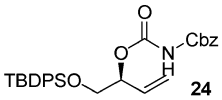
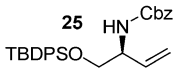
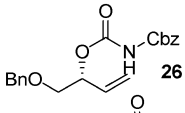
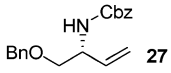
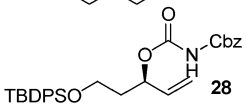
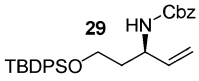
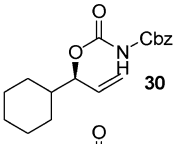
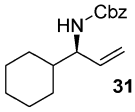
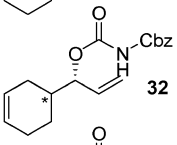
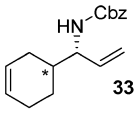
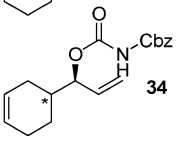
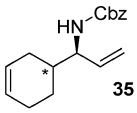


Table 1. Ir(I)-Catalyzed Decarboxylative Allylic Amidation of Chiral Branched Benzyl Allyl Imidodicarboxylates[a]

entry	substrate	*ee* of substrate (%)	time (h)	products	yield[b] (%)	B/L[c]	*ee* of product[d] (%)
1	 **17**	96	0.5	 **18**	90	>95:01	96
2	 **19**	>99	0.5	 **20**	89	>95:01	>99
3	 **21**	>99	0.5	 **15**	85	>95:01	>99[e]
4	 **22**	98	0.5	**23** 	88	>95:01	98
5	 **24**	>99	0.5	**25** 	86	>95:01	>99
6	 **26**	>99	0.5	 **27**	87	>95:01	>99
7	 **28**	>99	0.5	**29** 	85	>95:01	>99
8	 **30**	>99	0.5	 **31**	80	>95:01	>99
9	 **32**	98	0.5	 **33**	82	>99:01	98[f]
10	 **34**	>99	0.5	 **35**	80	>95:01	>99[f]

[a] All reactions were performed at 0.2 mmol scale. [b] Isolated yields. [c] Ratios of branched and linear regioisomers were determined by ^{1}H NMR of crude reaction mixtures. [d] Enantiomeric excesses (ee's) were determined by using chiral HPLC. [e] ee was determined by conversion to *N*-Cbz-protected L-phenylalanine. [f] Contains two diasteromers due to the additional stereocenter (the carbon with *).

In summary, the highly stereospecific decarboxylative allylic amidation reaction of chiral branched benzyl allyl imidodicarboxylates has been developed, and the reaction is effected by $[Ir(COD)Cl]_2$, a chiral phosphoramidite ligand **L***, and DBU in THF at room temperature. Since the reaction is believed to proceed by the double inversion mechanism involving the Ir-π-allyl intermediate, complete chirality transfer has been observed. The developed stereospecific decarboxylative allylic amidation of **7** and *ent*-**7** is nicely complementary to the corresponding decarboxylative allylic amidation of **1**. Since these two decarboxylative allylic amidations can provide *N*-Cbz (one of the most popular nitrogen protection groups)-protected chiral allylic amines, they are in turn complementary to the stereoselective allylic aminations[9−12] and amidations (for the formation of *N*-Boc-/Ts-/Ns-protected chiral allylic amines)[13,14] developed by other

(6) An achiral catalytic system involving $[Ir(COD)Cl]_2$ and $P(OPh)_3$, which was used for the allylic amination (ref 9), was not effective for the reaction, and the addition of a base such as DBU and Et_3N was fruitless.

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research groups and us, and should be of particular value in the asymmetric synthesis of chiral allylic amines and more complex nitrogen-containing compounds.[15]

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Supporting Information Available: Complete experimental procedures for all new compounds and ^{1}H and ^{13}C spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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