

Iridium(I)-catalyzed regio- and enantioselective allylic amidation

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Received 5 July 2007; revised 27 July 2007; accepted 1 August 2007

Available online 6 August 2007

Abstract—Ir(I)-catalyzed intermolecular allylic amidation of ethyl allyl carbonates with soft nitrogen nucleophiles under completely ‘salt-free’ conditions is described. A combination of [Ir(COD)Cl]₂, a chiral phosphoramidite ligand **L**^{*}, and DBU as a base in THF effects the reaction. The reaction appears to be quite general, accommodating a wide variety of R-groups and soft nitrogen nucleophiles, and proceeds with excellent regio- and enantioselectivities to afford the branched N-protected allylic amines. The developed reaction was conveniently utilized in the asymmetric synthesis of *N*-Boc protected α- and β-amino acids as well as (–)-cytoxazone.

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Ir(I)-catalyzed stereoselective allylic amination reactions have quickly become a method of choice for the preparation of optically enriched allylic amines due to their mild reaction conditions, as well as high regio- and enantioselectivity.^{1–5} As an alternative and complementary approach, we recently reported that a catalytic system involving [Ir(COD)Cl]₂, a chiral phosphoramidite ligand **L**^{*}, DBU, and proton sponge (PS) in THF enabled highly regio- and enantioselective decarboxylative allylic amidation of substituted allyl benzyl imidodicarbonylates **1** to the branched *N*-Cbz protected allylic amines **2**, and the catalytic reaction was likely to proceed through the Ir-π-allyl complex (Eq. 1 in Fig. 1).^{6,7} Three possible pathways are conceivable for the carbon–nitrogen bond formation step in the reaction (Eq. 2 in Fig. 1). Oxidative addition of **1** to the Ir(I) catalyst gives rise to intermediate **I**, which after proton shift from the nitrogen to the oxygen attacks the Ir-π-allyl complex to form the carbon–nitrogen bond. Alternatively, intermediate **I** can undergo decarboxylation to generate intermediate **II**, where the anion of benzyl carbamate acts as a nucleophile toward the Ir-π-allyl complex. The third possibility is an intermolecular reaction between the Ir-π-allyl complex and the anion of **1** generated in the reaction.

We were interested in developing the intermolecular version of the above decarboxylative allylic amidation reaction, and envisioned that pathways **I** and **III** could be mimicked by reactions between ethyl allyl carbonates **3** and di-benzyl imidodicarboxylate (or other soft nitrogen nucleophiles) in the presence of a base and the iridium catalyst, whereas the reaction between **3** and benzyl carbamate under similar conditions would follow pathway **II** (Fig. 2).

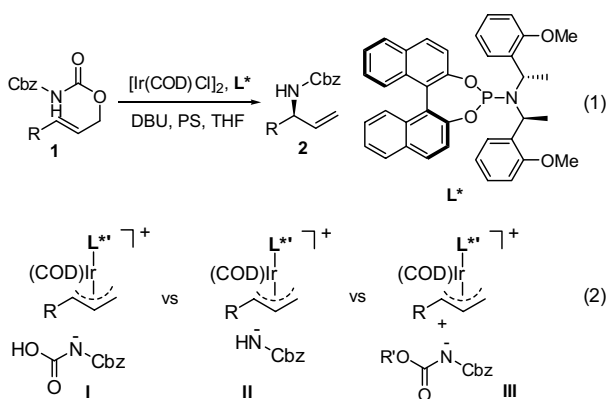


Figure 1. Ir(I)-catalyzed decarboxylative allylic amidation reaction of allyl benzyl imidodicarbonates and three possible reaction pathways.

Keywords: Iridium; Phosphoramidite ligand; Asymmetric amidation; α-Amino acid; β-Amino acid; Cyttoxazone.

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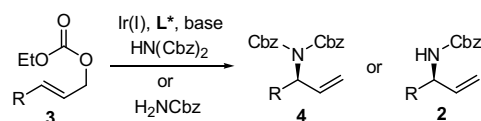


Figure 2. Ir(I)-catalyzed intermolecular allylic amidation.

Herein, we disclose that the Ir(I)-catalyzed intermolecular enantioselective allylic amidation reaction occurs between ethyl allyl carbonates **3** and di-benzyl imidodicarboxylate (or other soft nitrogen nucleophiles) in the presence of DBU to give the corresponding branched *N*-bis-Cbz protected allylic amine **4** (or *N*-bis-Boc/*N*-Ac,*N*-Boc protected allylic amines) in good to excellent yield and stereoselectivity (Fig. 2 and Table 1). So far, to the best of our knowledge, there has been only one literature report on the Ir(I)-catalyzed enantioselective allylic amidation reaction, which can give *N*-Ac, *N*-Cbz, and *N*-Boc (arguably three most popular *N*-protection groups) protected chiral allylic amines.⁸ While we were preparing the present paper, Helmchen's group reported a similar work on the enantioselective allylic amidation. Based on all data reported to date, our catalytic systems involving Ir(I), **L***, and DBU appear to be more general than the Helmchen's, accommodating a variety of alkyl/aryl groups and soft nitrogen nucleophiles such as (Ac)(Boc)NH, (Boc)₂NH, (Cbz)(Boc)NH, and (Cbz)₂NH, especially under 'salt-free' conditions.⁸

An allylic amidation reaction was initially performed on ethyl *trans*-hex-2-enyl carbonate (**3a**) using [Ir(COD)Cl]₂ (2 mol %), a chiral phosphoramidite ligand **L*** (4 mol %), the anion of benzyl carbamate (generated in situ from benzyl carbamate and *n*-BuLi at 0 °C) as a nucleophile (1.2 equiv), and DBU as a base (1 equiv) in THF (0.5 mL). Not even a trace amount of the desired product was observed, and the starting materials were recovered. All efforts using other counterions for the anion of benzyl carbamate, other solvents, and halide anions proved to be fruitless.⁹

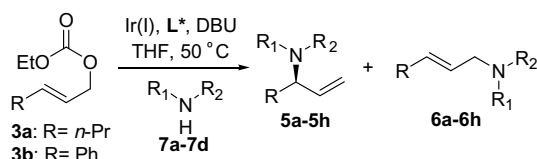
However, when *N*-acetyl *N*-*tert*-butyl carbamate (**7a**)¹⁰ was used as a nucleophile, the corresponding branched allylation product **5a** formed in 60% yield after 5 h with excellent regio- and enantioselectivities. Increasing the reaction temperature to 55 °C improved the reaction

yield to 95% and reduced the reaction time to 30 min without affecting regio- and enantioselectivities. Subsequently, the amount of DBU was adjusted to 20 mol % without any detrimental effects on reaction yield as well as regio- and enantioselectivities (entry 1 of Table 1). The determined optimal conditions were applied to ethyl cinnamyl carbonate (**3b**) (the corresponding cinnamyl benzyl imidodicarboxylate was a slower and more difficult substrate in the decarboxylative allylic amidation reaction under similar conditions), and the allylic amidation occurred equally well to give the branched product **5b** (entry 2).

Other soft nitrogen nucleophiles such as di-*tert*-butyl imidodicarboxylate (**7b**), benzyl *tert*-butyl imidodicarboxylate (**7c**),¹¹ and di-benzyl imidodicarboxylate (**7d**)¹¹ were examined with both ethyl *trans*-2-hexenyl carbonate and ethyl cinnamyl carbonate. All these reactions proceeded well to give the corresponding branched allylation products in high yields and excellent regio- and enantioselectivities (entries 3–6). In the case using **3a** and **7d**, a lower reaction temperature (room temperature) was necessary to suppress the transesterification reaction between the branched allylation product **5g** and ethoxide anion generated in the reaction (entry 7). The reaction of **3b** with **7d** was sluggish at room temperature, and gave a mixture of the transesterification product and the usual allylation product (entry 8).

Selective/mono deprotections of the different nitrogen protecting groups of **5a–g** were studied (Scheme 1). Selective deprotection of the Boc group of **5a–5b** was effected by TFA in CH₂Cl₂, while selective deprotection of the acetyl group was achieved by K₂CO₃ in MeOH. Mono deprotection of the Boc groups of **5c–d** was accomplished by Zn in refluxing MeOH.¹² Similarly, treatment of either K₂CO₃ in MeOH or TFA in CH₂Cl₂ could be used for selective/mono deprotection of the Cbz/Boc groups of **5e–g**.

Table 1. Allylic amidation of ethyl allyl carbonates with different imidodicarboxylates^a



Entry	Carbonate	Nucleophile	Product	Time (h)	Yield ^b (%)	5/6 ^c	% ee of 5 ^d
1	3a	7a : R ₁ = Ac- R ₂ = Boc	5a	0.5	95	97:03	96
2	3b		5b	1.0	94	>99:01	>99
3	3a	7b : R ₁ = Boc- R ₂ = Boc	5c	0.5	93	98:02	96
4	3b		5d	1.0	90	>99:01	>99
5	3a	7c : R ₁ = Cbz- R ₂ = Boc	5e	0.5	94	98:02	96
6	3b		5f	1.0	92	>99:01	>99
7	3a	7d : R ₁ = Cbz- R ₂ = Cbz-	5g	3.0 ^e	90	99:01	96
8	3b		5h	f	f	f	f

^a All reactions were performed at 0.2 mmol scale.

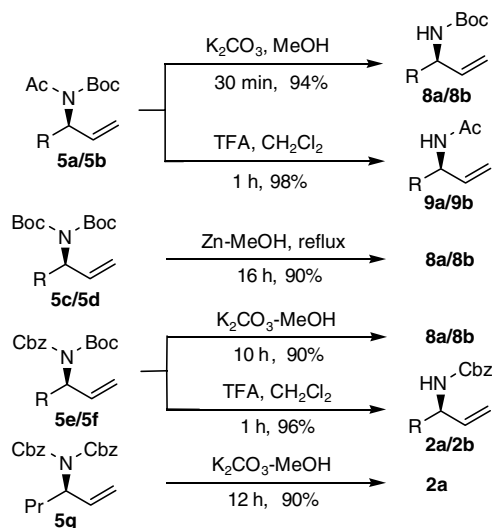
^b Isolated yields.

^c Ratios of regioisomers were determined by ¹H NMR of crude reaction mixtures.

^d Enantiomeric excesses (ee's) were determined by converting **5** to their mono *N*-Cbz/Boc derivatives and using chiral HPLC (Chiracel OD-H).

^e The reaction was conducted at room temperature.

^f See the text part.



Scheme 1. Selective/mono deprotections of the different nitrogen protection groups.

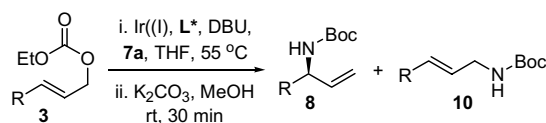
Having established the reaction conditions for the allylic amidation and deprotection reactions, we pursued an one-pot operation of two reactions. The allylation reaction between **7a** and **3a** in THF at 55 °C followed by the addition of K_2CO_3 and MeOH at room temperature furnished the corresponding *N*-Boc protected allylic amine **8a** in reaction yield and stereoselectivities comparable to those from the corresponding two step reactions.

The generality of the one-pot allylic amidation and deprotection sequence was probed with **7a** as a nitrogen nucleophile and a variety of different ethyl allyl carbonates, and the results were summarized in Table 2. According to the data, the Ir(I)-catalyzed allylic amidation and selective deprotection sequence appears to be quite general, tolerating a wide variety of substituents such as linear and branched alkyl (entries 1 and 2), conjugated alkenyl (entry 3), heteroatom functionalized alkyl (entry 4), aryl (entries 5 and 6), and heteroaryl groups (entries 7 and 8). In all cases, the *N*-Boc protected branched allylic amines **5** were obtained in high yields and excellent regio- and enantioselectivities.

To explore a synthetic utility of *N*-Boc protected chiral allylic amines and to ascertain their stereochemistry, compound **11** (from entry 5 of Table 2) was converted to the known α - and β -amino acids **12** and **14** as depicted in Scheme 2. The oxidative cleavage of **11** by $RuCl_3$ and $NaIO_4$ ¹³ produced *N*-Boc protected (*R*)-(-)-phenylglycine (**12**).¹⁴ On the other hand, the hydroboration–oxidation¹⁵ of **11** followed by oxidation of the resulting alcohol **13** by $RuCl_3$ and $NaIO_4$ gave *N*-Boc protected β -amino acid **14**.¹⁶

As shown in Scheme 3, combined with the Sharpless dihydroxylation reaction,¹⁷ the developed allylic amidation reaction could also provide a convenient route for the asymmetric synthesis of (-)-cytozoxone,¹⁸ a novel cytokinin modulator isolated from *Streptomyces* sp.¹⁹ The dihydroxylation reaction of the *N*-Boc protected

Table 2. One-pot allylic amidation and deprotection using methyl tert-butyl imidodicoxylate as a nitrogen nucleophile^a



Entry	R=	Time (h)	Yield ^b (%)	8/10 ^c	ee of 8 (%)
1		0.5	95	97:03	97 ^d
2		1.5	85	99:01	>99 ^e
3		0.5	92	98:02	96 ^e
4		0.5	94	99:01	99 ^e
5		1.0	94	>99:01	>99 ^d
6		1.0	92	>99:01	>99 ^d
7		1.0	85	>99:01	98.5 ^d
8		1.0	80	97:03	nd ^f

^a All reactions were performed at 0.2 mmol scale.

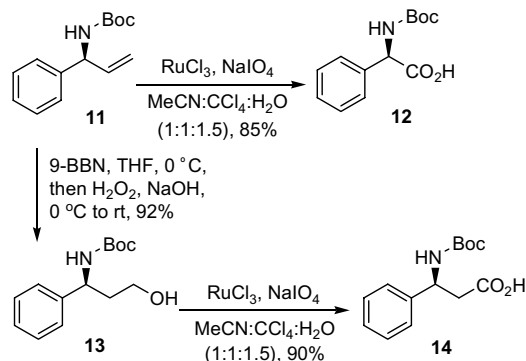
^b Isolated yields.

^c Ratios of regioisomers were determined by ¹H NMR of crude reaction mixtures.

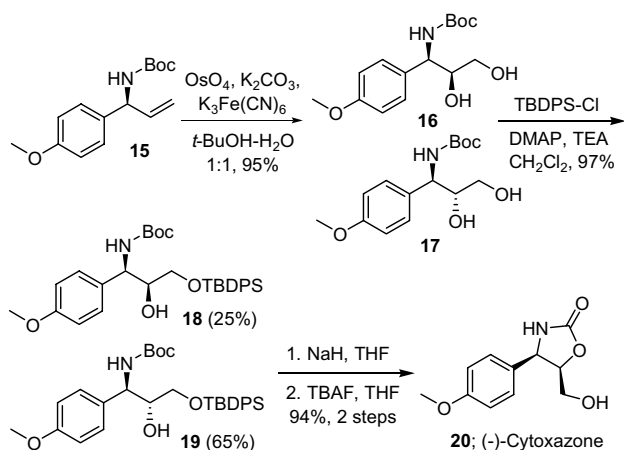
^d Enantiomeric excesses were determined using chiral HPLC.

^e Enantiomeric excesses were determined after converting to the respective Cbz derivatives.

^f The racemic compound could not be separated on HPLC using chiral columns OD-H, OJ-H, and OB-H in repeated attempts.



Scheme 2. Synthesis of *N*-Boc protected α - and β -amino acids.



Scheme 3. Asymmetric synthesis of (-)-cytoxazone.

allylic amine **15** (from entry 6 of Table 2) generated an inseparable mixture of *syn*- and *anti*-diols **16** and **17** in the ratio of 3:7. The use of the (DHQD)₂-PHAL/(DHQ)₂-PHAL ligand in the dihydroxylation reaction did not affect the *syn*/*anti*-ratio in any meaningful way. Thus, the diol mixture was converted to the corresponding TBDPS ethers **18** and **19**, which were separated by column chromatography. Upon treatment with NaH in THF, **19** cyclized to form the *O*-TBDPS protected (-)-cytoxazone, and the final deprotection of the TBDPS group by TBAF provided (-)-cytoxazone (**20**) in 53% overall yield in five steps starting from the corresponding achiral ethyl allyl carbonate.

In summary, a highly regio- and enantioselective intermolecular allylic amidation reaction has been developed, which employs [Ir(COD)Cl]₂, a chiral phosphoramidite ligand **L**^{*}, and DBU in THF. The reaction operates under completely ‘salt-free’ conditions, and proves to be quite general, accommodating a wide variety of allylic substrates and nitrogen nucleophiles. Also shown is the possibility of one pot operation of the allylic amidation reaction and subsequent selective/mono deprotection reaction. Since the developed allylic amidation reaction can provide the *N*-Ac, *N*-Boc, and *N*-Cbz (three popular nitrogen protection groups) protected chiral allylic amines, it is nicely complementary to the stereo-

selective allylic aminations developed by other research groups^{2–5} and should be of particular value in the asymmetric synthesis of nitrogen-containing chiral compounds.

Acknowledgments

Financial support from National Institute of Health (GM 08194) and The Welch Foundation (AX-1534) is gratefully acknowledged. We are also grateful to Dr. K. Ditrach, BASF, Germany, for a generous gift of a chiral amine for the synthesis of ligand **L**^{*}.

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