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Communication

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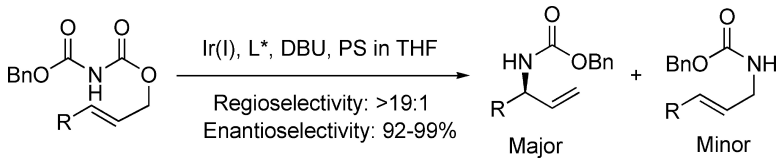

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Iridium(I)-Catalyzed Regio- and Enantioselective Decarboxylative Allylic Amidation of Substituted Allyl Benzyl Imidodicarbonates

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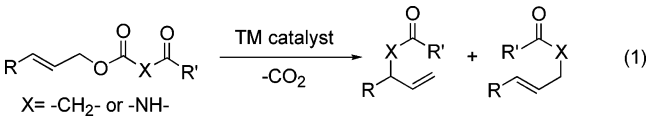
Transition-metal-catalyzed stereoselective allylic substitution has provided an important and convenient tool for carbon−carbon and carbon−heteroatom bond formation in organic synthesis[1] and is still evolving to include more diverse allylic electrophiles, nucleophiles, and catalysts. Of particular interest is the recent development of transition-metal-catalyzed *decarboxylative* allylic substitution reactions.[2] Ru and, particularly, Pd metals have been employed, and synthetically useful levels of regio- and enantioselectivities have been achieved in the decarboxylative allylation reaction of allyl β-ketoacetate derivatives (X = $-CH_2-$ in eq 1). However, given the well-known fact that carbamic acids can undergo facile decarboxylation, it is rather surprising that the analogous decarboxylative allylic amidation (X = −NH− in eq 1) has never been realized. To the best of our knowledge, there has been only one report for the decarboxylative carbon−nitrogen bond formation, where Tunge et al. described Pd-catalyzed decarboxylative allylic amination, albeit reaction stereochemistry was not an issue.[3] Herein, we describe the first iridium(I)-catalyzed highly regio- and enantioselective decarboxylative allylic amidation reaction of substituted allyl benzyl imidodicarbonates (X = −NH− in eq 1).

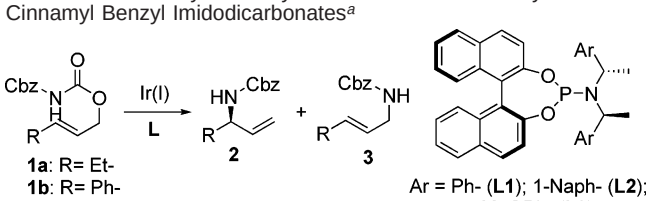


(1)

Literature analysis on regio- and enantioselective allylic amination[4−7] revealed that reaction conditions involving $[Ir(COD)Cl]_2$, a phosphoramidite ligand such as **L1**−**L3**, and THF solvent could be a good starting point for the decarboxylative allylic amidation, and a base was required to generate the active catalyst.[8] This led us to examine the effectiveness of various tertiary amines like TEA, DIPEA, DMAP, DABCO, DBU, and DBN in the decarboxylative allylic amidation reaction of 2-pentenyl benzyl imidodicarbonate (**1a**) by $[Ir(COD)Cl]_2$ and chiral phosphoramidite **L3** in THF. As shown in entries 1 and 2 of Table 1, respectively, only with DBN and DBU the reaction proceeded to give the decarboxylative allylation products **2a** and **3a** in a good yield and with an excellent regioselectivity, while the other amines either failed to react or gave only a trace amount of products (<5%). DBU was further investigated, and 1 equiv of DBU was found to be optimal in terms of both reaction time and regioselectivity (entries 2−5 in Table 1). Next, the effects of different ligands (**L1**, **L2**, and **L3**) and solvents (THF, Et_2O, EtOH, CH_2Cl_2, and DMF) were studied, and a combination of **L3** and THF resulted in the fastest reaction and highest regioselectivity (entries 2 and 6−9).

As an initial attempt to validate the generality of the found reaction conditions, cinnamyl benzyl imidodicarbonate (**1b**) was tested, but disappointingly branched product **2b** was obtained only in 20% yield after 24 h (entry 10 of Table 1). Therefore, we sought additives to improve reaction time and yield. The addition of metal

Table 1. Decarboxylative Allylic Amidation of 2-Pentenyl- and Cinnamyl Benzyl Imidodicarbonates[a]



entry	substrate	base(s) (mol %)	solvent	ligand	conversion[b] (%), reacn time (h)	2/3[b]	ee of 2 (%)
1	**1a**	DBN (100)	THF	**L3**	100, 1	98:02	
2	**1a**	DBU (100)	THF	**L3**	100, 1	98:02	
3	**1a**	DBU (10)	THF	**L3**	100, 1	95:05	
4	**1a**	DBU (50)	THF	**L3**	100, 1	96:04	
5	**1a**	DBU (500)	THF	**L3**	100, 2	95:05	
6	**1a**	DBU (100)	THF	**L1**	98, 16	93:07	
7	**1a**	DBU (100)	THF	**L2**	100, 1	95:05	
8	**1a**	DBU (100)	Et_2O	**L3**	98, 24	94:06	
9	**1a**	DBU (100)	EtOH	**L3**	94, 24	89:11	
10	**1b**	DBU (100)	THF	**L3**	<20, 24	ND	
11	**1b**	DBU (100) PS (100)	THF	**L3**	100, 1	>99:1	>99

[a] 0.2 mmol scale with $[Ir(COD)Cl]_2$ (2 mol %) and **L** (4 mol %) in THF (0.5 mL) at room temperature. [b] Based upon ^1H NMR of the crude reaction mixture.

salts (LiCl, LiBr, CuI, $ZnBr_2$, etc.) did not help.[9] However, surprisingly, proton sponge (PS) increased the reaction rate by >100-fold, and excellent regio- and enantioselectivities were obtained (entry 11). Both DBU and PS were found to be necessary for the reaction, since the reaction did not proceed to completion in the absence of either.

The scope of the iridium(I)-catalyzed regio- and enantioselective decarboxylative allylic amidation was examined with a variety of substituted allyl benzyl imidodicarbonates, and the results were shown in Table 2. The decarboxylative allylic amidation appears to be quite general accommodating a wide range of substituents such as linear and branched alkyl (entries 1−4), conjugated alkenyl (entry 5), aryl (entry 6), heteroaryl (entry 7), heteroatom-functionalized alkyl (entries 8 and 9), and isolated alkenyl groups (entries 10 and 11). For the sterically more hindered (entries 3 and 4) and/or slow substrate (entry 9), higher catalyst load (4 mol %) and temperature (55 °C) were necessary to ensure good reaction yields as well as high regio- and enantioselectivities.

To probe the reaction mechanism, a crossover experiment was conducted with a 1:1 mixture of **4** and **5** to determine the intra- vs intermolecular nature of the reaction. Crossover products **7** and **8** formed along with usual products **6** and **9** in almost equal amounts (eq 2). This result is more consistent with the reaction mechanisms involving the Ir−π-allylic intermediate over intramolecular [3,3]-rearrangement (eq 3). Combined with the fact that the stereochemical outcome of the allylic amidation is the same as that of the allylic amination by **L**,[6,7] the results of the crossover experiment further suggest that the actual nucleophile in the reaction may be

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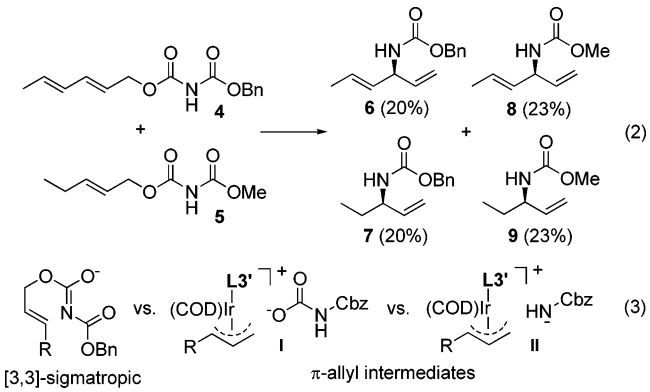
Table 2. Ir-Catalyzed Enantioselective Decarboxylative Allylic Amidation of Substituted Allylic Benzyl Imidodicarbonates

Entry	Substrate (R-)	Reaction condition[a]	Time (h)	Yield (%)[b]	**b**/**l**[c]	*ee* of **b** (%)[d]
1		A	1	92	98:02	94
2		A	2	90	97:03	96
3		B	1	85	90:10	96
4		B	1	85	98:02	96
5		A	3	80	98:02	92
6		A	1	90	>99:01	>99
7		A	3	70	97:03	94
8		A	12	80	98:02	98
9		B	1	78	98:02	99
10		A	3	86	96:04	96
11		A	3	85	95:05	95

[a] Reaction condition A: substrate (0.2 mmol), $[Ir(COD)Cl]_2$ (2 mol %), **L3** (4 mol %), DBU (1 equiv), PS (1 equiv), THF (0.5 mL) at room temperature. Reaction condition B: same as the condition A except $[Ir(COD)Cl]_2$ (4 mol %) and **L3** (8 mol %) at 55 °C. [b] Isolated yield of **b** and **l**. [c] Ratio of regioisomers determined by ^1H NMR of the crude reaction mixture. [d] Enantiomeric excess determined by chiral HPLC.

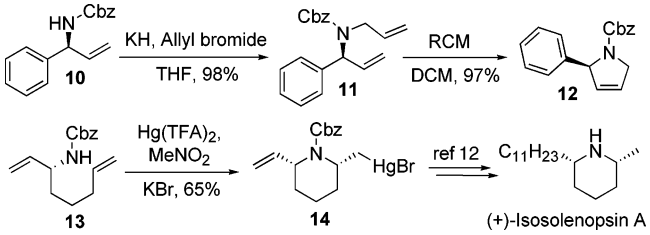
completely liberated from the Ir−π-allylic complex and then attack the complex *anti* to iridium.



To shed light on the nature of the actual nucleophile and/or timing of decarboxylation (**I** vs **II** in eq 3), ethyl cinnamyl carbonate was treated with benzyl carbamate anion (generated in situ from benzyl carbamate and *n*-BuLi at 0 °C) under the reaction conditions. No product was observed even in trace, and all starting materials were recovered. Hence, it might be unlikely that the benzyl carbamate anion acts as the actual nucleophile to the Ir−π-allylic complex (**II** in eq 3). Rather, the carboxylate anion (after proton shift from the nitrogen to the oxygen), which is generated from the oxidative addition of the substrate to the Ir catalyst, attacks the Ir−π-allylic complex (**I** in eq 3) and decarboxylation occurs later in the reaction sequence. This is in sharp contrast to the decarboxylative allylic carbon−carbon bond formation where decarboxylation takes place prior to the attack of a nucleophile to the π-allyl complex.[2c]

To demonstrate the synthetic utility of Cbz-protected chiral allylic amines generated and to establish absolute stereochemistry at the allylic carbon, compounds **10** and **13** were converted to **12** and **14**,

Scheme 1



respectively; analytical data of which matched with those of the corresponding known compounds (Scheme 1). Compound **10** was N-alkylated by KH and allyl bromide to give diene **11**, which upon ring closing metathesis (RCM) by Grubbs second generation catalyst[10] transformed to **12**.[11] The intramolecular amidomercuration reaction of **13** with $Hg(TFA)_2$ in nitromethane afforded **14**, which was previously used as a synthetic precursor for the stereoselective synthesis of (+)-isosolenopsin A.[12]

In conclusion, we have successfully developed the iridium(I)-catalyzed highly regio- and enantioselective decarboxylative allylic amidation reaction, which is quite general and proceeds under mild reaction conditions. This, combined with the synthetic utility of optically pure Cbz-protected allylic amines, should make the developed decarboxylative allylic amidation of particular value in organic synthesis.

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

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