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Sequential Catalytic Isomerization and Allylic Substitution. Conversion of Racemic Branched Allylic Carbonates to Enantioenriched Allylic Substitution Products

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We report a sequence of two catalytic processes occurring through metal−allyl intermediates that leads to enantioselective substitution of branched allylic esters with nitrogen, oxygen, and carbon nucleophiles. This process lies at the intersection of developments in sequential catalytic processes[1] and the challenge of controlling both regioselectivity and enantioselectivity in allylic substitution. Enantioselective allylic substitution of branched allylic electrophiles is desirable because these reagents are easily prepared from a vinyl Grignard reagent and the wide array of available aldehydes.

Iridium-catalyzed enantioselective allylic substitution of *linear* allylic electrophiles has become a powerful tool to prepare optically active allylic amines and ethers,[2−9] but iridium-catalyzed reactions of *branched* allylic electrophiles occur with low enantioselectivities.[7,9] Reactions of racemic, branched isomers of monosubstituted allylic esters catalyzed by Mo[10] and W[11] complexes form enantioenriched branched substitution products, but no examples of Mo- or W-catalyzed enantioselective allylic substitutions with heteroatom nucleophiles have been reported. A few examples of Pd- and Rh-catalyzed enantioselective allylic substitutions of monosubstituted allylic esters have been reported to form products in high enantiomeric excess, but these methods are either restricted in the scope of substrates that react with high regio- and enantioselectivity[12] or use ligands that are cumbersome to synthesize.[13]

The alternative approach reported here involves a sequence of Pd-catalyzed isomerization and Ir-catalyzed enantioselective substitution of the resulting linear isomer. This sequence forms allylic substitution products from cinnamyl and dienyl carbonates and acetates in high yields, with high regioselectivities, and with high enantiomeric excess.

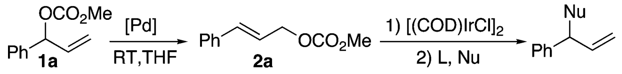
Our studies on the Pd-catalyzed isomerization are summarized in Table 1. Oxidative addition of allylic carbonates and acetates to Pd(0) is reversible and can cause isomerization of the allylic esters.[14] Pd(II) complexes also catalyze rearrangements of allylic esters and imidates.[15] Thus, we tested both Pd(0) and Pd(II) complexes for a productive process to generate linear allylic esters for use in crude form in the Ir-catalyzed allylation of nitrogen, oxygen, and carbon nucleophiles. Because the Ir-catalyzed reactions occur in high enantiomeric excess in THF solvent, it was necessary to develop a Pd-catalyzed process in this medium. Entries 1−7 show the effect of the identity of the palladium catalyst on the rate of isomerization. The reactions catalyzed by $Pd(PPh_3)_4$ (entry 2) were much faster than those catalyzed by $(CH_3CN)_2PdCl_2$ (entry 1), but a palladium complex lacking excess PPh_3 would be more desirable because PPh_3 could complex to the $[(COD)IrCl]_2$ [7] catalyst precursor or the active cyclometalated Ir(I) species[4,6] and interfere with the subsequent Ir-catalyzed allylic substitution. Thus, we tested combinations of PPh_3 and $Pd(dba)_2$ as catalyst for the isomerization, and the Pd complex generated from a mixture of 0.2 mol % of $Pd(dba)_2$ and 0.4 mol % of PPh_3 led to complete isomerization of **1a** to **2a** over a convenient time period (entry 4). Lower ratios of PPh_3 to Pd (entry 5) and lower loadings of Pd and PPh_3 led to incomplete isomerization (entry 6). Isomerizations catalyzed by Pd on carbon in the absence of any ligand or by $Pd(PPh_3)_4$−polystyrene were slow (entries 7 and 8).

Table 1. Optimization of Reaction Conditions for Conversion of Branched Carbonate to Linear Carbonates[a]

entry	[Pd] (%)	L (%)	time (h)	yield[b] (%) of **2**
1	$(CH_3CN)_2PdCl_2$ (1)		24	95
2	$Pd(PPh_3)_4$ (1)		0.6	100
3	$Pd(dba)_2$ (0.5)	PPh_3 (1.0)	0.5	100
4	$Pd(dba)_2$ (0.2)	PPh_3 (0.4)	3.0	100
5	$Pd(dba)_2$ (0.2)	PPh_3 (0.3)	12	60
6	$Pd(dba)_2$ (0.1)	PPh_3 (0.2)	24	70
7	Pd/C (1)		12	10
8	$Pd(PPh_3)_4$−poly (0.5)		12	20

[a] All reactions were conducted with **1a** (1 M) in THF at room temperature. [b] GC yield.

Scheme 1



Experiments to combine the isomerization step with allylic substitution were conducted with the combination of $Pd(dba)_2$ (0.2 mol %) and PPh_3 (0.4 mol %) as catalyst. Addition of the iridium catalyst and benzylamine to the crude reaction solution formed only 10% of the allylic amine. However, simple filtration of the crude isomerization product through silica to remove the bulk of the palladium catalyst, followed by addition of the iridium catalyst and benzylamine, led to formation of the substitution products in high yield and enantioselectivity (Table 2, entry 1). The scope of the sequential isomerization and enantioselective allylic substitution of branched, racemic allylic esters is summarized in Table 2. The Ir-catalyzed process was conducted with three different phosphoramidites: **L1**, which first gave high enantiomeric excesses for allylic amination, the naphthyl analogue **L2** that improved regio- and enantioselectivity in some cases,[5] and **L3**, the ligand with edited stereochemistry.[6,8]

In many cases, high yield and selectivities were observed for the amination reactions when using **L3**, although certain reactions required **L2** to occur with high selectivities. For example, reactions of electron-poor cinnamyl carbonates (entries 5−7), dienyl carbonates (entries 10 and 11), and a cinnamyl acetate (entry 8) occurred in higher yield in the presence of the catalyst generated from **L2** than from the catalyst generated from **L3**. The branched carbonate **1a** isomerized to the linear isomer in 3 h at room temperature, and the crude allylic carbonate reacted over 6 h with the amines after addition of the iridium catalyst.

Electron-poor allylic carbonates **1b**−**e** also underwent the sequential catalytic process to give the optically active allylic amines in good yields with high regio- and enantioselectivities when **L2**

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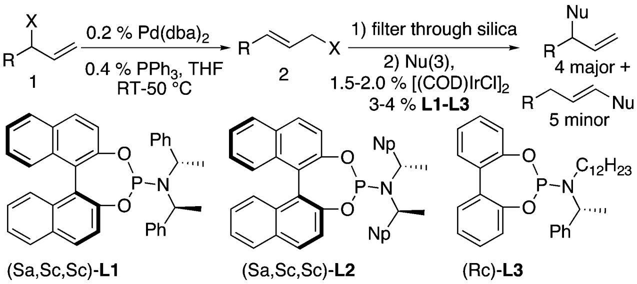
Table 2. Enantioselective Allylic Substitution of Branched Electrophiles

entry	R, X (**1**)	Nu (**3**)	L	yield[b] (%)	**4**/**5**[c]	ee[d] (%)
1	C_6H_5, OCO_2Me (**1a**)	$PhCH_2NH_2$ (**3a**)	**L3**	76	98/2	93
2	C_6H_5, OCO_2Me (**1a**)	morpholine (**3b**)	**L3**	89	98/2	94
3	C_6H_5, OCO_2Me (**1a**)	$PhNH_2$ (**3c**)	**L3**	83	98/2	94
4	2-FC_6H_4 OCO_2Me (**1b**)	morpholine (**3b**)	**L2**	81	99/1	82
			L3	63	99/1	82
5	3-$OMeC_6H_4$, OCO_2Me (**1c**)	morpholine (**3b**)	**L2**	82	99/1	95.5
6	4-$CF_3C_6H_4$, OCO_2Me (**1d**)	morpholine (**3b**)	**L2**	72	99/1	94
7	4-ClC_6H_4, OCO_2Me (**1e**)	morpholine (**3b**)	**L2**	83	99/1	96
8[e−g]	4-$OMeC_6H_4$ OAc (**1f**)	$PhCH_2NH_2$ (**3a**)	**L1**	75	99/1	87
			L2	83	99/1	94
			L3	77	99/1	86
9[e−g]	2-thienyl, OAc (**1g**)	$PhCH_2NH_2$ (**3a**)	**L3**	79	98/2	93
10[g,h]	$CH_3CH{=}CH$, OCO_2Me (**1h**)	$PhCH_2NH_2$ (**3a**)	**L2**	57	98/2	88
11[g,i]	$(CH_3)_2CHCH{=}CH$, OCO_2Me (**1i**)	$PhCH_2NH_2$ (**3a**)	**L2**	70	96/4	88
12[j,k]	C_6H_5 OCO_2Me (**1a**)	LiOPh (**3d**)	**L1**	76	90/10	94
			L3	62	85/15	92
13[j]	C_6H_5 OCO_2Me (**1a**)	$NaCH(CO_2Me)_2$ (**3f**)	**L1**	77	97/3	94
			L3	72	80/20	91

[a] All reactions were carried out with 1 mmol of **1** and 1.2 mmol of **3** in THF (1.0 mL) at room temperature in the presence of 0.002 mmol $Pd(dba)_2$, 0.004 mmol PPh_3, 0.015 mmol $[(COD)IrCl]_2$, and 0.030 mmol of **L1**−**L3** unless otherwise noted. [b] Average of isolated yields from two runs. [c] Determined by ^1H NMR spectra of crude reaction mixtures. [d] Determined by chiral HPLC. [e] Isomerization was performed at 60 °C. [f] EtOH (0.4 mL) was used as cosolvent. [g] $[(COD)IrCl]_2$ (0.020 mmol) and **L1**−**L3** (0.040 mmol) were used. [h] $Pd(dba)_2$ (0.4%) and PPh_3 (0.8%) were used for isomerization. [i] $Pd(dba)_2$ (0.3%) and PPh_3 (0.6%) were used for isomerization. [j] THF (2.0 mL) was used. [k] **3d** (2 mmol) was used.

Scheme 2



was used as ligand (entries 4−7). The Pd-catalyzed isomerization of electron-poor, branched allylic carbonates (**1b**−**e**) to the corresponding linear carbonates was slightly slower than the isomerization of the neutral carbonate **1a**. However, the allylic amination product was obtained in 6 h from the isomerized linear carbonates.

Reactions of electron-rich cinnamyl esters were initiated with acetate, rather than carbonate, leaving groups because the electron-rich carbonates were unstable toward silica gel purification. Although the Pd-catalyzed isomerization of electron-rich branched allylic acetates (**1f**,**g**) was slower (6−12 h at 60 °C) than the isomerization of the allylic carbonates (**1a**−**e**), the subsequent allylic amine products were obtained in good yields with high regio- and enantioselectivities. For example, the product from reaction of *p*-methoxy-substituted **1f** and benzylamine was obtained in 94.4% ee when **L2** was used as ligand (entry 8). The product from reaction of thienyl derivative **1g** with benzylamine in the presence of the catalyst containing **L3** formed the allylic amine product in 93% ee (entry 9). Dienyl carbonates **1h**,**i** underwent the catalytic isomerization and allylic substitution to give optically active amines in moderate yield and good enantioselectivities (entries 10 and 11).

The isomerization and substitution sequence was also suitable for the synthesis of allyl aryl ethers and allylic malonates. These etherification and alkylation reactions catalyzed by Ir complexes of **L1** formed higher ratios of **4** to **5** than reactions catalyzed by Ir complexes of **L3**. Carbonate **1a** underwent the combination of isomerization and substitution with lithium phenoxide (entry 12) to form the branched allyl aryl ether in 76% yield, 9:1 regioselectivity, and 94% ee with the catalyst containing **L1**. Good enantioselectivity was also observed for reactions conducted with **L3**. The isomerization of **1a**, followed by reaction with sodium dimethylmalonate (entry 13) in the presence of the iridium catalyst containing ligand **L1**, also formed the corresponding branched allylic malonate with high regioselectivity and enantioselectivity.

In conclusion, we have developed a catalytic protocol for the conversion of readily accessible branched aromatic allylic esters to branched allylic products in good yield with high regio- and enantioselectivity with a broad range of nucleophiles. This procedure is based on a complementary, sequential use of allylpalladium and allyliridium chemistry, the palladium-catalyzed reaction for isomerization, and the iridium-catalyzed reaction for enantioselective C−N, C−O, and C−C bond formation.

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Supporting Information Available: Full experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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