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Complete Retention of *Z* Geometry in Allylic Substitution Catalyzed by an Iridium Complex

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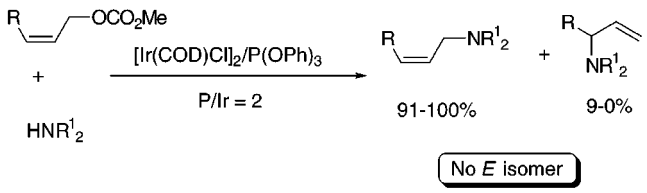
ABSTRACT



The *Z* geometry of methyl (*Z*)-3-monosubstituted-2-alkenyl carbonate was completely retained in iridium complex-catalyzed allylic amination. The reaction of methyl (*Z*)-2-nonenyl carbonate with piperidine in the presence of a catalytic amount of $[Ir(COD)Cl]_2$ and $P(OPh)_3$ at 50 °C for 2 h gave a 98:2 mixture of (*Z*)-1-(2-nonenyl)piperidine and 1-(1-*n*-hexyl-2-propenyl)piperidine in 86% yield. No *E* isomer was obtained. Various (*Z*)-allylic amines were obtained in 91–100% selectivity by allylic amination of methyl (*Z*)-3-monosubstituted-2-alkenyl carbonate.

The chemistry of (π-allyl)metal complexes is central in organic synthesis.[1] The reaction of a (π-allyl)metal complex with a nucleophile provides various synthetically useful processes. One of the important aspects of the chemistry of (π-allyl)metal complexes is syn−anti isomerization[2] via a $\pi-\sigma-\pi$ process which greatly affects the regio- and stereoselectivity of allylic substitution. Nucleophilic attack at the unsubstituted allylic terminus of a terminally monosubstituted syn π-allyl complex gives an (*E*)-alkene, while that of an anti π-allyl complex gives a (*Z*)-alkene.

A wide variety of transition-metal complexes are reported to be a catalyst for allylic substitution. Of the metal complexes studied, palladium is the most general and versatile catalyst.[3] It is well-known that a syn (π−allyl)-palladium complex is thermodynamically more stable than an anti complex.[4] (π−Allyl)palladium complexes undergo a rapid syn−anti isomerization prior to the nucleophilic attack. Thus, palladium complex catalyzed allylic substitution of (*Z*)-3-monosubstituted-2-alkenyl esters resulted in the loss of *Z* geometry.[5] A mixture of (*E*)- and (*Z*)-alkenes is obtained. A limited example of the retention of *Z* geometry has been reported.[6] Åkermark found that 2,9-disubstituted-1,10-phenanthroline could induce a preference for the anti configuration and reported *Z*-selective allylic alkylation of (*Z*)-2-hexenyl acetate.[7] (*Z*)-Alkene was obtained in moderate

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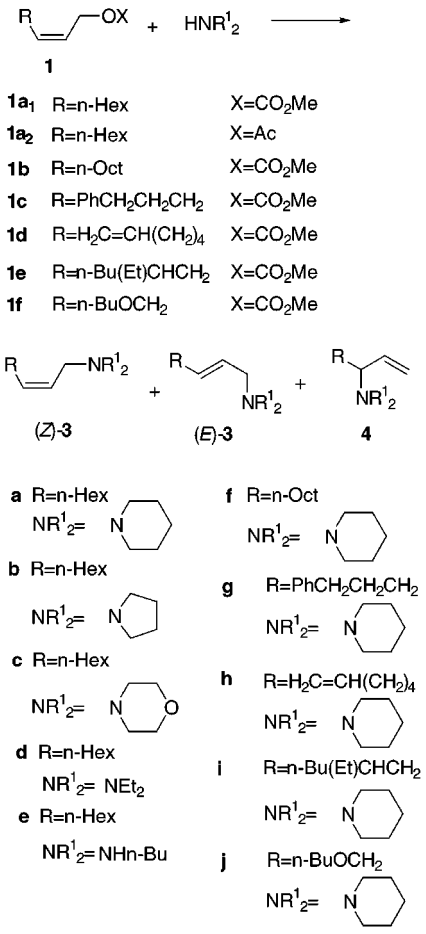
to good selectivity, but the formation of (*E*)-alkene could not be suppressed completely.

We reported that an iridium complex is a new and efficient catalyst for allylic alkylation.[8] The regioselectivity of iridium complex catalyzed allylic alkylation depends on the geometry of the allylic system, i.e., the regioselectivity of alkylation of a syn (π-allyl)iridium intermediate is different from that of an anti (π-allyl)iridium intermediate. The alkylation occurred prior to syn−anti isomerization. This result prompted us to investigate *Z*-selective allylic substitution. We first succeeded with the complete retention of *Z* geometry in the allylic amination[5a,c,9] of (*Z*)-3-monosubstituted-2-alkenyl carbonate (Scheme 1).

Scheme 1



The reaction of methyl (*Z*)-2-nonenyl carbonate (**1a$_1$**) with piperidine in the presence of a catalytic amount of [Ir(COD)Cl]$_2$ and P(OPh)$_3$ gave a mixture of (*Z*)-**3a** and **4a**. The reaction using piperidine as a solvent at 50 °C for 2 h gave a 98:2 mixture of (*Z*)-**3a** and **4a** in 86% yield (Table 1; entry 1).[10] No *E* isomer was obtained. A large excess of piperidine was necessary for high yield. The reaction of 5 equiv of piperidine with **1a$_1$** at reflux in THF for 24 h gave products in 14% yield (entry 2). The starting material was recovered in 80% yield. P(OPh)$_3$ was the most efficient ligand. The use of P(OEt)$_3$ and PPh$_3$ decreased the yield of products (entries 3 and 4). The ratio of P to Ir was also important. The reaction of 1 or 2 equiv of P(OPh)$_3$ with Ir gave products in good yield (entries 1 and 6), while that of 3 equiv of P(OPh)$_3$ with Ir resulted in a slight decrease of the yield (entry 7). [Ir(COD)$_2$]BF$_4$/P(OPh)$_3$ and [Ir(COD)OMe]$_2$/P(OPh)$_3$ showed comparable catalytic activities and selectivities (entries 9 and 10). Carbonate was more reactive than acetate. The reaction of (*Z*)-2-nonenyl acetate (**1a$_2$**) with piperidine gave a decrease in the yield of products at prolonged reaction time (entry 8).

The reactions of **1a$_1$** with various amines were examined (Table 2). Amines were used as a solvent. Allylic amines (*Z*)-**3b**−**e** were obtained in 94−98% selectivity. No *E* isomer was obtained. The structure of the amine had a substantial

Table 1. Reaction of **1a** with Piperidine[a]

entry no.	substrate	catalyst[b]	P/Ir	time/h	yield/%[c]	(*Z*)-**3a**/(*E*)-**3a**/**4a**[d]
1	**1a$_1$**	A/P(OPh)$_3$	2	2	86	98/0/2
2[e]	**1a$_1$**	A/P(OPh)$_3$	2	24	14	92/0/8
3	**1a$_1$**	A/P(OEt)$_3$	2	24	7	96/0/4
4	**1a$_1$**	A/PPh$_3$	2	24	31	8/78/14
5	**1a$_1$**	A	0	23	15	100/0/0
6	**1a$_1$**	A/P(OPh)$_3$	1	2	88	98/0/2
7	**1a$_1$**	A/P(OPh)$_3$	3	4	69	97/0/3
8	**1a$_2$**	A/P(OPh)$_3$	2	24	43	97/0/3
9[f]	**1a$_1$**	B/P(OPh)$_3$	2	2	90	97/0/3
10[g]	**1a$_1$**	C/P(OPh)$_3$	2	3	83	97/0/3

[a] A mixture of **1a** (2 mmol), [Ir(COD)Cl]$_2$ (0.04 mmol), ligand, and piperidine (5 mL) was stirred under argon at 50 °C. [b] Catalyst legend: A, [Ir(COD)Cl]$_2$: B, [Ir(COD)$_2$]BF$_4$; C, [Ir(COD)OMe]$_2$. [c] Isolated yield. [d] Determined by GLC. [e] Piperidine (10 mmol) in refluxing THF (5 mL). [f] Catalyst 0.04 mmol. [g] Catalyst 0.04 mmol.

Table 2. Reaction of **1a$_1$** with Amines[a]

entry no.	amine	product	yield/%[b]	(*Z*)-**3**/(*E*)-**3**/**4**[c]
1[d]	pyrrolidine	**3b**, **4b**	71	94/0/6
2[e]	morpholine	**3c**, **4c**	83	95/0/5
3[f]	diethylamine	**3d**, **4d**	62	98/0/2
4[g]	*n*-butylamine	**3e**, **4e**	23	96/0/4

[a] A mixture of **1a$_1$** (2 mmol), [Ir(COD)Cl]$_2$ (0.04 mmol), P(OPh)$_3$ (0.16 mmol), and amine (5 mL) was stirred under argon at 50 °C. [b] Isolated yield. [c] Determined by GLC. [d] Reacted for 3 h. [e] Reacted for 24 h. [f] [Ir(COD)Cl]$_2$ (0.08 mmol) and P(OPh)$_3$ (0.32 mmol). Reacted for 4 h. [g] Reacted for 3 h.

(8) (a) Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647. (b) Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 263.

(9) For Pd complex catalyzed allylic amination, see: (a) Åkermark, B.; Åkermark, G.; Hegedus, L. S.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037. (b) Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 3584.

(10) **General Procedure for Allylic Amination of Allylic Esters**. A typical procedure is described for the reaction of **1a$_1$** with piperidine. A mixture of methyl (*Z*)-2-nonenyl carbonate (**1a$_1$**; 400 mg, 2.0 mmol), triphenyl phosphite (49.6 mg, 0.16 mmol), [Ir(COD)Cl]$_2$ (26.9 mg, 0.04

effect on the yield of products. The reactions of **1a$_1$** with secondary amines gave the corresponding products in good yield (entries 1−3). In contrast to results obtained in the reactions with secondary amines, the reaction of **1a$_1$** with *n*-butylamine decreased the yield considerably (entry 4). Bulky amines are therefore necessary for high yields of (*Z*)-**3**.[11]

As shown in Table 3, (*Z*)-**1b**−**f** were successfully reacted with piperidine to give (*Z*)-**3f**−**j** with high selectivities. No *E* isomer was obtained. Terminal alkene was tolerated in the allylic amination. The reaction of **1d** with piperidine was regiospecific to give (*Z*)-**3h** in 89% yield (entry 3). The steric congestion around the carbon−carbon double bond affected the reaction time and the yield of the product. The reaction of **1e** with piperidine for 22 h gave (*Z*)-**3i** exclusively in 33% yield. Increasing the amount of the catalyst to 8 mol % accelerated the reaction to give (*Z*)-**3i** in 70% yield (entry 4). The alkoxy functionality was also tolerated and did not alter the regio- and stereoselectivity of the allylic amination; allylic amine (*Z*)-**3j** was obtained with 98% selectivity (entry 5).

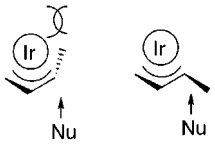
Table 3. Reaction of **1** with Piperidine[a]

entry no.	substrate	product	time/h	yield/%[b]	(*Z*)-**3**/(*E*)-**3**/**4**[c]
1	**1b**	**3f, 4f**	8	83	94/0/6
2	**1c**	**3g, 4g**	15	81	91/0/9
3	**1d**	**3h, 4h**	3	89	100/0/0
4[d]	**1e**	**3i, 4i**	5	70	100/0/0
5	**1f**	**3j, 4j**	4	78	98/0/2

[a] A mixture of **1** (2 mmol), $[Ir(COD)Cl]_2$ (0.04 mmol), $P(OPh)_3$ (0.16 mmol), and piperidine (5 mL) was stirred under argon at 50 °C. [b] Isolated yield. [c] Determined by GLC. [d] $[Ir(COD)Cl]_2$ (0.08 mmol) and $P(OPh)_3$ (0.32 mmol).

As seen in allylic alkylations,[8a] the selectivity of the allylic amination depends on the geometry of the allyl system. The reaction of (*E*)-**1a$_1$** with piperidine at 50 °C for 2 h gave a 28:1:71 mixture of (*E*)-**3a**, (*Z*)-**3a**, and **4a** in 93% yield. The *syn*-(π-allyl)- and *anti*-(π-allyl)iridium intermediates gave different results. This difference in regioselectivity is reasonably explained as follows. When the amine approaches the substituted allylic terminus of the *anti*-(π-allyl)iridium intermediate, the substituent and iridium moiety are close together and thereby increase steric repulsion (Scheme 2).[12]

Scheme 2



The transition state of the amination at the substituted allylic terminus of the *anti*-(π-allyl)iridium intermediate is therefore less stable than that of the *syn*-(π-allyl)iridium intermediate. Thus, amination of the *anti*-(π-allyl)iridium intermediate preferentially occurs at the unsubstitued allylic terminus.

In summary, we have succeeded with the complete retention of *Z* geometry in the allylic amination. This unique feature of iridium catalysis will have wide synthetic application.

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Supporting Information Available: Text giving experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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mmol), and piperidine (5.0 mL) was stirred at 50 °C for 2 h under an Ar atmosphere. The progress of the reaction was monitored by GLC. After **1a$_1$** was consumed, the reaction mixture was diluted with ether. The ethereal solution was extracted with 6 M HCl. The combined acidic layers were neutralized with NaOH and extracted with ether. The organic layer was dried with $MgSO_4$ and filtered. After evaporation of the solvent, the residue was purified by column chromatography (*n*-hexane/ethyl acetate (70/30)) to give (*Z*)-**3a** and **4a** (360 mg; yield 86%). **(*Z*)-1-(2-Nonenyl)piperidine ((*Z*)-3a)**: ^{1}H NMR (400 MHz, C_6D_6) δ 1.00 (t, J = 7.0 Hz, 3H), 1.30−1.51 (m, 10H), 1.66 (quintet, J = 5.1 Hz, 4H), 2.19 (q, J = 7.1 Hz, 2H), 2.48 (t, J = 5.1 Hz, 4H), 3.09 (d, J = 6.7 Hz, 2H), 5.64 (dtt, J = 11.0, 7.3, 1.6 Hz, 1H), 5.77 (dtt, J = 11.0, 6.7, 1.5 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0, 22.6, 24.4, 26.0 (2C), 27.4, 28.9, 29.5, 31.7, 54.5 (2C), 55.9, 126.4, 132.8. Anal. Calcd for $C_{14}H_{27}N$: C, 80.31; H, 13.00; N, 6.69. Found: C, 80.07; H, 13.01; N, 6.65. **1-(1-*n*-Hexyl-2-propenyl)piperidine (4a)**: Compound **4a** could not be isolated in pure form. A partial ^{1}H NMR spectrum was obtained from the mixture of (*Z*)-**3a**. ^{1}H NMR (400 MHz, C_6D_6): δ 5.12 (dd, J = 17.2, 2.2 Hz, 1H), 5.21 (dd, J = 10.3, 2.2 Hz, 1H), 5.83 (ddd, J = 17.2, 10.3, 6.9 Hz, 1H).

(11) Cone angles of secondary amines are larger than those of primary amines; see: Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520.

(12) See reference 8a and references therein.