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Regio- and Enantioselective Allylic Amination of Achiral Allylic Esters Catalyzed by an Iridium−Phosphoramidite Complex

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Enantioselective routes to optically active amines provide valuable synthetic building blocks.[1] The enantioselective preparation of chiral tertiary amines is particularly important because they cannot be generated directly by enantioselective hydrogenation of imines,[2,3] and the enantioselective hydrogenation of enamines remains a challenge.[4] In addition, methods for enantioselective coupling of two fragments by C−N bond-formation are limited.[5−8] We recently reported catalysts for enantioselective hydroaminations to form allylic and benzylic amines.[6,7] Because η^3-π-benzyl and -allyl complexes are intermediates in both our hydroamination chemistry and allylic amination, we sought to develop, in parallel, catalysts for enantioselective allylic substitution.

During these studies we took notice of chiral phosphoramidites **6**−**8**, designed by Feringa and co-workers (Figure 1).[9,10] Their π-accepting property should be favorable for nucleophilic attack on allyl or benzyl groups. Indeed, their complexes with palladium showed activity during our preliminary studies on hydroamination, and as reported here, complexes with iridium show high activity and selectivity for enantioselective substitution of (*E*)-cinnamyl and terminal aliphatic allylic carbonates. These allylic aminations are conducted with air-stable catalyst components at ambient temperatures.

Allyic substitution of acyclic allylic electrophiles catalyzed by W,[11] Mo,[12,13] Ru,[14,15] Ir,[16] and Rh[17,18] complexes often generate the chiral branched substitution products. Enantioselective amination of symmetrical 1,3-diphenylallyl carbonates,[19−23] and unsymmetrical branched allylic acetates,[24] along with a single example of palladium-catalyzed asymmetric amination of a terminal allylic ester or carbonate,[25] have been reported.[26] However, a general, enantioselective allylic amination from an achiral, terminal allylic electrophile has not been accomplished. Takeuchi[27] and Evans[28] have shown that iridium and rhodium complexes of achiral phosphites catalyze the formation of branched amines, in some cases with conservation of enantioselectivity.[28] Helmchen reported enantioselective alkylation of branched allylic acetates with modest ee's[29] in the presence of an iridium−phosphoramidite catalyst. Analogous enantioselective aminations occurred with ee's below 15%. Iridium complexes that may be related to the amination chemistry were isolated.[30]

In contrast, we have found that iridium complexes of phosphoramidite (R_a,R_C,R_C)-**6** in Figure 1 catalyze allylic amination with high activity to form branched product **3** with high enantioselectivity (Scheme 1). Regioselective formation of **3** required control of the reaction conditions. In EtOH, the phosphoramidite complex catalyzed allylic transposition of the amino group in product **3**: in the presence of $[Ir(cod)Cl]_2$ (1 mol %) and (R_a,R_C,R_C)-**6** (2 mol %, L/Ir = 1), the reaction of cinnamyl methyl carbonate (**1a**) with morpholine (**2g**, 3.0 equiv) gave complete conversion and excellent

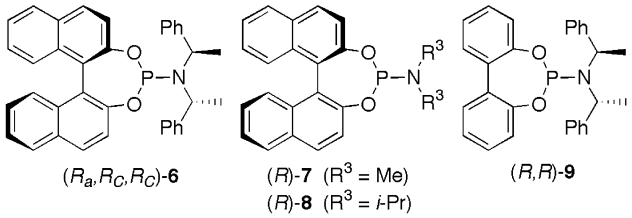
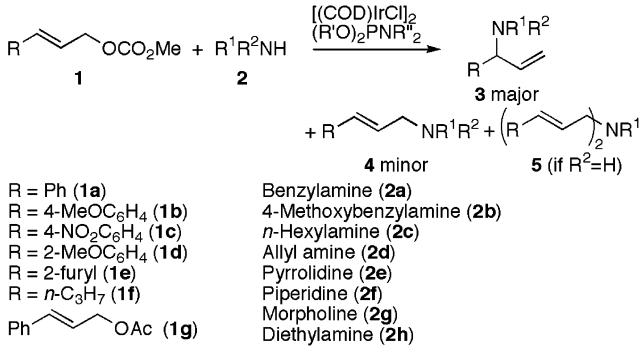


Figure 1. Phosphoramidite ligands used in this study.

Scheme 1



regioselectivity (**3**/**4** = 99/1) after 1 h at room temperature but produced lower ratios of **3**/**4** (**3**/**4** = 67/33 after 12 h and 23/77 after 24 h) and the more stable **4** as the major product (**3**/**4** = 10/90) after 60 h.

Solvent influenced the reactivity, regioselectivity, and enantioselectivity for the reaction of 1.2−1.3 equiv of benzylamine (**2a**) with **1a**. The reactivity at room temperature followed the order DMF, EtOH (100% conversion after 1−2 h) > MeOH, THF, CH_3CN (8−10 h) > CH_3NO_2, DME (20−24 h) > CH_2Cl_2, NEt_3 (48 h) > 1,4-dioxane, Et_2O, toluene (reactions were incomplete after 72 h). Reactions in each solvent, except NEt_3 and CH_3NO_2, occurred with high regioselectivity (**3**/**4**/**5** = 98−94/1−4/0−3) when 1.2−1.3 equiv of amine was used. The enantioselectivity of reactions in different solvents followed the order THF, Et_2O (95% ee), DME (94% ee) > toluene, 1,4-dioxane, CH_2Cl_2 (92−90% ee) > NEt_3 (86% ee) > DMF, EtOH, CH_3CN (80−77% ee) > CH_3NO_2 (65% ee) > MeOH (52% ee). Reactions in the polar solvents DMF, EtOH, and MeOH were fast, but low ee's were observed. Reactions in THF displayed the most suitable balance of rate and enantioselectivity.

The effect of ligand and temperature on selectivity is summarized in Table 1. The reaction proceeded smoothly at room temperature in the presence of $[Ir(cod)Cl]_2$ (1 mol %) and (R_a,R_C,R_C)-**6** (2 mol %, L/Ir = 1) to give after 10 h branched **3** with excellent regioselectivity (**3**/**4**/**5** = 98/1/1) and 84% isolated yield of product with 95% enantiomeric excess (entry 1). Reaction at 50 °C for 4 h gave 89% of **3** with 94% ee (entry 2). Reactions catalyzed by

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Table 1. Ligand and Temperature Effects for Ir-Catalyzed Enantioselective Allylic Amination of **1a** with **2a**[a]

entry	ligand	temp	time (h)	**3**/**4**/**5**[b]	yield of **3** (%)[c]	% ee[d]
1	(R_a,R_C,R_C)-**6**	rt	10	98/1/1	84	95 (*R*)
2	(R_a,R_C,R_C)-**6**	50 °C	4	98/2/0	89	94 (*R*)
3	(S_a,R_C,R_C)-**6**	50 °C	72	93/6/1	66	75 (*S*)
4	(*R*)-**7**	50 °C	72	41/43/16	11	0
5	(*R*)-**8**	50 °C	72	72/23/5	25	61 (*R*)
6	(*R*,*R*)-**9**	rt	48	96/2/2	72	87 (*R*)

[a] The reaction was conducted with 1 mmol of **1a** and 1.2−1.3 mmol of **2a** in THF (0.5 mL) in the presence of 0.01 mmol of $[Ir(cod)Cl]_2$ and 0.02 mmol of phosphoramidite unless otherwise noted. [b] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [c] Isolated yield after silica gel chromatography. [d] Determined by HPLC with a Daicel Chiralcel OD-H column and hexane/2-PrOH/Et_2NH (99.74/0.25/0.01) as eluent.

Table 2. Enantioselective Allylic Amination Catalyzed by Ir−(R_a,R_C,R_C)-**6**[a]

entry	allyl carbonate	amine	time (h)	**3**/**4**/**5**[b]	yield of **3** (%)[c]	% ee[d]
1	**1a**	**2b**	18	99/0/1	80	94 (−)
2	**1a**	**2c**	9	98/2/0	88	96 (*R*)
3	**1a**	**2d**	12	na	76	97 (−)
4	**1a**	**2e**	2	98/2	75	97 (−)
5	**1a**	**2f**	10	97/3	91	96 (−)
6	**1a**	**2g**	24	99/1	92	97 (−)
7[e]	**1a**	**2h**	16	98/2	83	97 (−)
8	**1b**	**2a**	9	99/1/0	88	96 (−)
9[f]	**1c**	**2a**	12	83/13/4	67	86 (−)
10	**1d**	**2a**	16	95/4/1	77	76 (−)
11	**1e**	**2a**	10	96/2/2	58	97 (+)
12	**1f**	**2a**	10	88/8/4	66	95 (+)
13[g]	**1g**	**2a**	16	97/3/0	95	95 (−)
14[h]	**1g**	**2g**	72	96/4	87	96 (−)

[a] The reaction was conducted at room temperature with 0.02 mmol (R_a,R_C,R_C)-**6** as noted in Table 1. [b] Determined by ^{1}H NMR spectra of crude mixtures. [c] Isolated yield after silica gel chromatography. [d] Determined by HPLC. [e] Reaction conducted at 50 °C. [f] 2.0 equiv of **2a** was used. [g] Conducted in EtOH with 3.0 equiv of **2a**. [h] Conducted neat with 3.0 equiv of **2g**.

complexes of the ligand diastereomer (S_a,R_C,R_C)-**6** were slow, even at 50 °C, and formed the opposite enantiomer in 66% yield and 75% ee (entry 3). Complexes of binaphthol derived ligands with achiral and smaller substituents at nitrogen, (*R*)-**7** and (*R*)-**8**, produced lower ee's than did those of (R_a,R_C,R_C)-**6** (entries 4 and 5). Ligand (*R*,*R*)-**9**[31] with a biphenol unit gave product with a lower, though substantial enantioselectivity of 87% (entry 6).

The scope of the allylic amination catalyzed Ir−(R_a,R_C,R_C)-**6** is summarized in Table 2. Reactions of **1a** with primary amines such as 4-methoxybenzylamine (**2b**), *n*-hexylamine (**2c**), and allylamine (**2d**) gave the corresponding branched allylic amine **3** with high selectivity over the isomeric **4** or diallylamine **5** (entries 1−3) and with enantioselectivities from 94 to 97%. Cyclic secondary amines, such as pyrrolidine (**2e**), piperidine (**2f**), and morpholine (**2g**), reacted at room temperature (entries 4−6) to form the branched allylic amines with enantioselectivities between 96 and 97%. The acylic diethylamine reacted at 50 °C to form the branched product in high yield and 97% ee (**2h**, entry 7).

Other aromatic and heteroaromic derivatives of carbonate **1a** also reacted with **2a** in high yield and enantioselectivity. *p*-Methoxycinnamyl methyl carbonate (**1b**) reacted with **2a** to form branched **3** with 88% yield and 96% ee (entry 8). Furanyl **1e** formed **3** in acceptable yield and excellent enantioselectivity (entry 11). Perhaps most impressive, the complex of (R_a,R_C,R_C)-**6** catalyzed the allylic amination of (*E*)-2-hexenyl methyl carbonate (**1f**, entry 12) with high enantioselectivity. Although the yield was moderate because of slightly lower regioselectivity, the enantiomeric excess was 95%. The reaction also occurred with cinnamyl acetate **1g** in ethanol (entry 13) or neat (entry 14) with 3.0 equiv of amine to form the allylic amine in good yield and with excellent enantioselectivity.

Two terminal carbonates reacted less selectively. *p*-Nitrocinnamyl **1c** was only slightly soluble in THF and gave lower regioselectivity and enantioselectivity (86% ee, entry 9). *o*-Methoxy-substituted cinnamyl carbonate **1d** reacted with high regioselectivity, but the branched product formed with only 76% ee (entry 10). Branched allylic carbonates have, thus far, reacted to give low ee's of branched allylic amine after full conversion.

In conclusion, we developed a new catalytic process to produce branched aromatic or aliphatic secondary or tertiary allylic amines in high yield with excellent enantioselectivity from achiral allylic actetates and carbonates. The terminal olefin in the product can be used to generate, for example, 1,3-amino alcohols, 1,3-diamines, and various types of amino acids. Mechanistic understanding and further evaluation of substrate scope will comprise future studies.

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Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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