Synthesis of Allylic Amines

Enantioselective Allylation of Aromatic Amines after In Situ Generation of an Activated Cyclometalated Iridium Catalyst**

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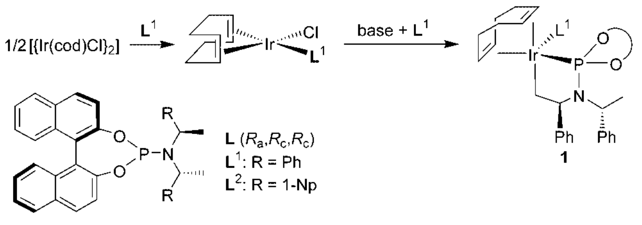
Aromatic amines with a stereocenter α to the nitrogen atom are important structural motifs in a number of biologically active compounds.[1] Many of approaches to such structures have been investigated, but each method has limitations. Thus, a highly enantioselective procedure to prepare optically active aromatic amines would be valuable, and an enantioselective route to *N*-aryl allylic amines would be particularly useful because of the dual functionality in these compounds.

Allylic substitution catalyzed by transition metals has emerged as a powerful tool for enantioselective formation of C–C, C–N, and C–O bonds.[2–4] However, aromatic amines have not been used commonly in allylic amination,[5–7] presumably because they are less nucleophilic than the more commonly used benzylamine or stabilized anionic nitrogen nucleophiles. A general and highly enantioselective reaction between an aromatic amine without an activating group on the nitrogen atom and an achiral allylic ester or a racemic branched allylic electrophile has not been reported.

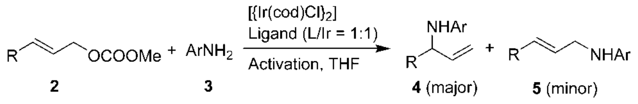
Catalysts based on metals other than palladium[8–16] and its congeners often form the more hindered, branched product from nucleophilic substitution with unsymmetrical monosubstituted allylic esters.[17–20] This reactivity complements the regioselectivity of palladium catalysts, which tend to form the linear products. We previously reported asymmetric allylic substitution of achiral allylic carbonates with aliphatic amines and phenoxides to form branched allylic amines and ethers with high regio- and enantioselectivities in the presence of an iridium complex with a phosphoramidite ligand.[21,22] Reactions of aromatic amines did not occur under the conditions developed originally.

Our mechanistic studies have shown that the cyclometalated complex **1**, generated in situ by treatment of $[\{Ir(cod)Cl\}_2]$ (cod = cycloocta-1,5-diene) and the ligand L^1 with an alkylamine base (Scheme 1), is likely to be the true catalyst in the allylic amination.[23] Reactions conducted with the isolated complex **1** as catalyst occurred faster and with broader scope than those with the combination of $[\{Ir(cod)Cl\}_2]$ and L^1.



Scheme 1. Synthesis of **1**; 1-Np = 1-naphthyl.

We proposed that the initial system failed to catalyze reactions of anilines because aromatic amines are not basic enough to induce cyclometalation, not because aromatic amines are too weakly nucleophilic to react with the iridium allyl intermediate.[23] If so, then the reactions of aniline should occur with a catalyst generated in situ by the action of a separate additive. Herein we report two convenient methods to generate the active catalyst in situ and the use of this catalyst to develop a general reaction of allylic carbonates with aromatic amines.[24] These reactions occur with a broad range of achiral, linear allylic carbonates to give branched chiral allyl aryl amines in excellent yields and with high regio- and enantioselectivities (Scheme 2).



Scheme 2. Amination of allylic carbonates **2** with aniline.

The cyclometalated complex **1** was generated in pure form by reaction of $[\{Ir(cod)Cl\}_2]$ and L^1 with an unhindered secondary amine, such as pyrrolidine (Scheme 1). We reasoned that the addition of a volatile primary amine prior to addition of aniline or a tertiary aliphatic amine would induce

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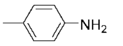
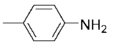
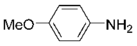
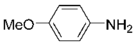
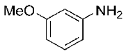
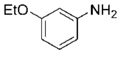
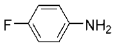
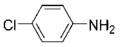
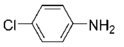
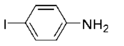
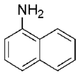
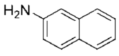
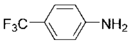
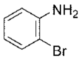
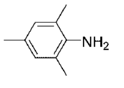
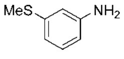
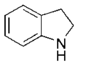
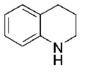
cyclometalation without interfering with the reaction of the aniline.

Thus, one procedure (method A) involved heating [{Ir(cod)Cl}$_2$] and L^1 with propylamine at 50 °C for 20 min. After evaporation of the volatile materials, the crude yellow solid **1** was dissolved in THF, and a portion or all of this solution was used as catalyst for the reactions of aromatic amines. As shown in Table 1, reactions of allylic carbonates with electron-rich as well as electron-neutral anilines in the presence of 2 mol % iridium catalyst occurred within 2–2.5 h, with high regioselectivities and enantioselectivities up to 98 %. Aromatic (**2a**) and aliphatic allylic carbonates (**2b**) reacted similarly.

Table 2: Optimization of the reaction conditions with a tertiary amine base as additive.

Ligand	Additives (equiv)	t [h]	Conv. [%]	Yield [%]	**3/4**	*ee* [%]
L^1 (2 %)	NEt$_3$ (0.50)	24	0	–	–	–
L^1 (2 %)	DABCO (0.50)	24	100	72	> 99:1	92
L^2 (1 %)	DABCO (0.50)	2	100	77	> 99:1	95
L^2 (1 %)	DABCO (0.10)	6	100	80	> 99:1	96

Table 1: Allylic amination of methyl cinnamyl carbonate (**2a**) and the methyl carbonate derived from (*E*)-2-hexen-1-ol (**2b**) with aromatic amines (see Scheme 2).

Entry	Carbonate **2**	Amine **3**	t [h]	**4**	Yield [%]	**4/5**	*ee* [%]	Method[a]
1	**2a**		6	**4b**	76	99:1	94	B
2	**2b**		2	**4c**	94	96:4	93	A
3	**2a**		4	**4d**	91	98:2	95	B
4	**2b**		2	**4e**	95	95:5	95	A
5	**2a**		4	**4f**	82	97:3	96	B
6	**2a**		2.5	**4g**	86	97:3	96	A
7	**2a**		10	**4h**	90	98:2	94	B
8	**2a**		10	**4i**	89	98:2	96	B
9	**2a**		2.5	**4i**	80	95:5	96	A
10	**2a**		10	**4j**	92	98:2	96	B
11	**2a**		10	**4k**	83	97:3	95	B
12	**2a**		10	**4l**	89	99:1	95	B
13	**2a**		16	**4m**	72	94:6	96	C
14	**2a**		16	**4n**	66	93:7	94	B
15	**2a**		2	**4o**	82	97:3	96	B
16	**2a**		2.5	**4p**	85	97:3	96	A
17	**2a**		2	**4q**	90	99:1	95	B
18	**2a**		2	**4r**	89	97:3	96	B

[a] Method A: The catalyst was generated from propylamine (3.6 mmol) upon heating with [{Ir(cod)Cl}$_2$] and L^1 at 50 °C for 20 min. The reactions were conducted on a 1.0-mmol scale in THF (0.5 mL) with a molar ratio for **2a**/**3**/[{Ir(cod)Cl}$_2$]/L^1 of 1:1.2:0.01:0.02. Method B: The catalyst was generated in situ with DABCO as additive. The reactions were conducted on a 1.0-mmol scale in THF (0.5 mL) at room temperature with a molar ratio for **2a**/**3**/DABCO/[{Ir(cod)Cl}$_2$]/L^2 of 100:125:10:0.5:1. Method C: The reactions were conducted as for method B, but with a molar ratio for **2a**/**3**/DABCO/[{Ir(cod)Cl}$_2$]/L^2 of 100:125:10:1:2.

Alternatively, the reaction was conducted at room temperature with a tertiary amine additive. We tested the reaction of methyl cinnamyl carbonate with aniline in the presence of tertiary amine additives (Table 2). The reaction in the presence of the relatively unhindered 1,4-diazabicyclo[2.2.2]octane (DABCO) gave the desired branched amine in high yield and with 92 % *ee*. The amount of DABCO influenced the reaction rate but did not significantly affect the enantioselectivity.

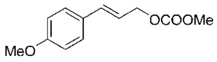
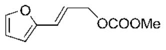
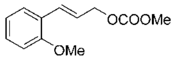
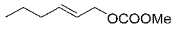
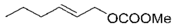
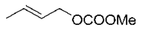
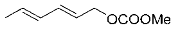
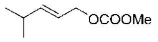
Further improvement in rate and selectivity was achieved by conducting reactions with the bulkier ligand L^2 (methods B and C Table 1). For example, the reaction of the hexenyl carbonate **2b** with aniline in the presence of the catalyst generated from L^2 occurred with 96 % *ee*, while the same reaction occurred with 92 % *ee* when the catalyst was generated from L^1.

The results with methods B and C show that the scope of the reaction of aromatic amines with aromatic and aliphatic carbonates with DABCO as additive is broad (Table 1). Electron-rich and electron-neutral aromatic amines reacted with allylic carbonates to generate the branched *N*-aryl allylic amines in high yields and with excellent regio- and enantioselectivities (entries 1, 3, 5, 7, 8, 10–12). Unhindered aromatic amines or sterically hindered primary aromatic amines, such as 2,4,6-trimethylaniline, reacted in high yields with excellent selectivities (entries 14, 15). The reaction of *o*-bromoaniline is noteworthy because the *ortho*-bromo substituent can be used for further transformations.[25] Cyclic secondary aromatic amines also reacted to give the branched *N*-allylamine in excellent yields (entries 17, 18), but acyclic secondary aromatic amines reacted with regioselectivities that ranged from 4:1 (in favor of the branched isomer) to 1:1.

Some electron-deficient aromatic amines required longer reaction times and higher catalyst loadings but formed the substitution product in acceptable yield and high enantioselectivity (Table 1, entries 13, 14). More electron-deficient anilines like *p*-cyanoaniline, did react, but in low yield and regioselectivity. The extremely electron-deficient *p*-nitroaniline did not react.

The scope of electrophile used encompassed both aromatic and aliphatic allylic carbonates (Table 3). In addition to the parent cinnamyl carbonate (**2a**), *p*-methoxy cinnamyl carbonate and the 2-furyl-substituted allylic carbonate reacted to give the branched products in excellent yields and selectivities (entries 1, 2).

Table 3: Amination of allylic carbonates **2** with aniline (Scheme 2, Ar = Ph).

Entry	Carbonate **2**	*t* [h]	**4**	Yield [%]	*ee* [%]	b/l **4/5**	Method[a]
1		10	**4s**	88	96	97:3	B
2		10	**4t**	81	90	94:6	B
3		10	**4u**	91	74	99:1	B
4		3	**4v**	87	95	98:2	B
5		2.5	**4v**	93	92	92:8	A
6		3	**4w**	72	95	97:3	B
7		3	**4x**	87	97	98:1:1[b]	B
8		16	**4y**	83	97	97:3	D[c]

[a] For conditions of methods A–C see footnote [a] to Table 1. [b] The ratio of α-branched/γ-branched/linear product. [c] Method D: The reaction was conducted with the catalyst generated in situ with DABCO as additive. The reaction was carried out on a 1.0-mmol scale in THF (0.5 mL) at room temperature with a relative mole ratio for **2a**/**3**/DABCO/[$\{Ir(cod)Cl\}_2$]/L^2 of 100:125:5:0.5:1.

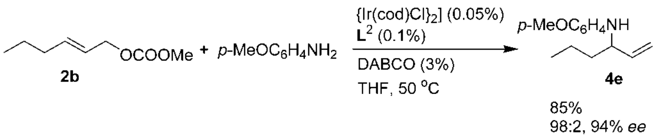
In contrast to most previous systems for allylic substitution, reactions of aliphatic allylic carbonates in the presence of the iridium-phosphoramidite catalyst occurred in high yield and with high regio- and enantioselectivities. Furthermore, the aliphatic carbonates reacted even faster than the aromatic carbonates. Thus, reactions of the methyl carbonates derived from (*E*)-2-hexen-1-ol and (*E*)-2-buten-1-ol with aniline were complete in 3 h and required only 5% DABCO additive (Table 3, entries 4, 6). In contrast, the reaction of methyl cinnamyl carbonate with aniline required 10 h under otherwise identical conditions. The methyl carbonate derived from (*E*,*E*)-2,4-hexadien-1-ol, a substrate recently explored by Helmchen and Lipowsky in allylic amination with alkyl and benzyl amines,[26] reacted with aniline to form the α-substituted **4x** with excellent regio- and enantioselectivities (entry 7).

Even aliphatic allylic carbonates with branching points α to the allyl unit reacted with high regio- and enantioselectivities. The branched allylic carbonate derived from (*E*)-4-methyl-2-penten-1-ol gave mostly linear product upon rhodium-catalyzed allylic amination. In contrast, reaction of the linear isomer of this allylic ester with aniline in the presence of 1 mol% of the iridium catalyst and 3 mol% DABCO formed the branched allylic amine **4y** with 97% *ee* and a branched-to-linear ratio of 97:3 (Table 3, entry 8).[27]

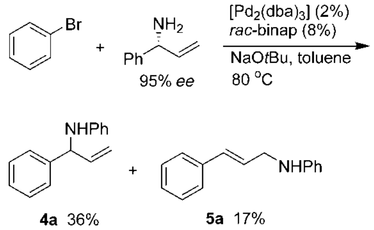
The unusually fast amination of aliphatic allylic carbonates allowed reactions of these substrates to be conducted with low catalyst loadings. For example, the reaction of carbonate **2b** with *p*-anisidine in the presence of 0.1 mol% of iridium catalyst afforded the allylic amine **4e** in 85% yield and with 94% *ee* (Scheme 3).

In contrast to these examples, *ortho*-methoxy cinnamyl carbonate reacted with aniline to give the substitution product with the same enantiomeric excess (74% *ee*) that was observed for reactions of this carbonate with aliphatic amines and phenoxides. Thus far, we have not solved the problem of enantioselective reactions of *ortho*-substituted allylic carbonates (Table 3, entry 3).

In principle, Pd-catalyzed cross-coupling[28–30] of an aromatic halide with an enantiopure α-chiral primary or secondary amine could be used to form the same α-chiral amines as those generated by this allylic substituiton. To compare aromatic amination to allylic amination as a method to prepare these materials, we conducted the reaction between phenyl bromide and an enantioenriched primary allylic amine (95% *ee*) catalyzed by a combination of [$Pd_2(dba)_3$] and (±)-binap (Scheme 4), which was shown previously[31] to couple an aryl bromide with optically active phenethylamine without racemization. In contrast to reactions of



Scheme 3. Reaction of carbonate **2b** with *p*-anisidine in the presence of iridium catalyst to afford the allylic amine **4e**.



Scheme 4. Reaction of PhBr with an enantioenriched primary allylic amine catalyzed by a combination of [$Pd_2(dba)_3$] and (±)-binap; dba = *trans*,*trans*-dibenzylidenacetone, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

phenethylamine, reaction of the allylic amine formed a 2:1 mixture of branched **4a** (83% *ee*) and linear **5a** products in a moderate combined yield (53%). Presumably, isomerization and partial racemization of the branched allylic amine by the Pd catalyst occurred before or after coupling. Thus, the allylic amination appears to be a superior method for the synthesis of *N*-aryl allylic amines.

In conclusion, we have developed the first convenient and highly selective allylic amination with "electron-neutral" aromatic amines that lack an activating group on the nitrogen atom. This process was developed by conversion of an iridium precatalyst into an active cyclometalated catalyst in the presence of an appropriate additive. This catalyst activation was either conducted in situ prior to addition of the aromatic amine or with DABCO additive in the presence of aniline. This reaction occurs with electron-neutral and electron-rich aromatic amine nucleophiles as well as aromatic or aliphatic allylic carbonates, and displays remarkable catalyst efficiency. Further studies on the reaction mechanism, as well as applications in synthesis, will be reported in due course.

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