Asymmetric Catalysis

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Iridium-Catalyzed Enantioselective Synthesis of Allylic Alcohols: Silanolates as Hydroxide Equivalents**

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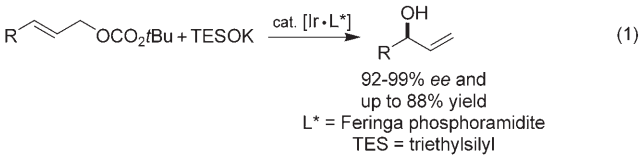
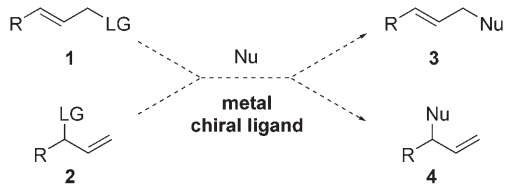
The development of efficient processes that give rapid and easy access to optically active building blocks is of great importance, particularly for the synthesis of complex molecules. The metal-catalyzed asymmetric allylic substitution reaction, which involves the addition of a range of diverse nucleophiles to an allylmetal intermediate, is one of the most studied processes.[1] The use of Ir complexes in this transformation provides access to products that are complementary to those obtained from Pd catalysis.[2,3] The types of nucleophiles that have been employed in Ir-catalyzed processes have included enolates derived from malonates, but recently other nucleophiles such as amines, phenols, and alkoxides have been used.[4–6] Omitted from this list is the use of hydroxide, or its equivalent, to give the corresponding product with a free alcohol. Herein, we describe the first example of an iridium-catalyzed enantioselective allylation involving the use of silanolates as nucleophiles, which allows convenient access to chiral allylic alcohols, useful building blocks in asymmetric synthesis [Eq. (1)]. The isolated products are formed in useful yields and 92–99% *ee*.



(1)

Over the last few years, iridium catalysis of asymmetric allylic substitution reactions has been the subject of considerable attention, because it allows access to chiral allylic products.[2,4–6] Its use offers a simple, complementary advantage over other methods, since it gives chiral, branched substitution products **4** from achiral, linear allylic derivatives **1**, whereas catalysis of the substitution reaction using palladium favors the linear, achiral adduct **3** from the same starting materials (Scheme 1). This reaction has led to excellent results using C, N, and O nucleophiles reported by the research groups of Hartwig,[4] Helmchen,[5] and Alexakis.[6]



Scheme 1. Transition-metal-catalyzed allylic substitution. LG = leaving group, Nu = nucleophile.

We have documented the use of chiral dienes as ligands in an Ir-catalyzed kinetic resolution of branched allylic carbonates using phenol as a nucleophile.[7] We have been searching to further expand the scope of nucleophiles that can be employed, with particular attention on the development of a process that employs water, or its equivalent, to give rise directly to allylic alcohols. This process became important to us for two reasons: a) the Ir-catalyzed allylic displacement reaction to give the secondary alcohol directly has not been reported to the best of our knowledge,[8] despite the fact that b) the resulting allylic alcohol adducts are amenable to further elaboration.[9] The methods reported to date that could in principle give rise to the free benzylic/allylic alcohols from an allylation process involve the use of the copper salt of benzyl alcohol.[4e,10] However, the chemoselective removal of the *O*-benzyl ether protecting group (**I**, Figure 1) from the products is difficult because of the presence of the C=C bond (**II**, Figure 1) as well as the potential for undesired hydrogenolytic cleavage of the benzylic/allylic C–O bond that defines the stereogenic center (**III**, Figure 1).

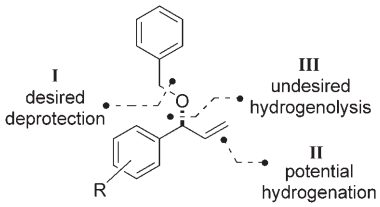


Figure 1. Potential selectivity problems during deprotection.

At the outset of our investigations we employed *tert*-butyl cinnamyl carbonate as a test substrate and examined its reaction with water in the presence of the catalyst derived from Feringa's phosphoramidite ligand[11] and iridium(I).[12] Despite repeated attempts at this reaction, no secondary alcohol was observed. We then screened a number of substrates equivalent to hydroxide, with specific interest in silanols, which appeared to be a particularly attractive class of nucleophiles.[13,14] Silanols can be considered as water surro-

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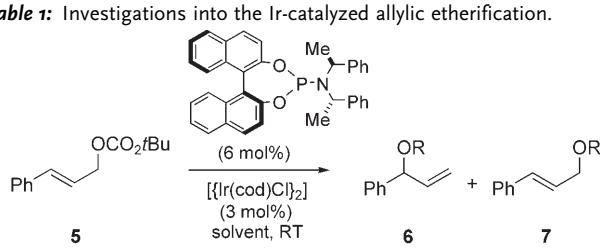
gates, because cleavage of the silyl ether is known to proceed under a variety of mild conditions.[15] Unfortunately, neither commercially available TMSOK nor TESOH led to the formation of any adducts (Table 1, entries 1 and 2). However, when using the corresponding potassium salt of the latter (TESOK) a promising result was obtained: the secondary silyl ether was formed in 39% yield and 96% *ee* (entry 3).[16] The modest yield was attributed to the poor regioselectivity (**6**/**7** 3:1). A range of different leaving groups were screened with the aim of optimizing the process, but all to no avail. Cinnamyl acetate led only to the formation of the undesired linear product **7**, and cinnamyl carbonates with small alkyl groups underwent alcoholate exchange in competition with etherification.

Table 1: Investigations into the Ir-catalyzed allylic etherification.



5 **6** **7**

Entry	Nucleophile	Solvent	Ratio **6**:**7**[a]	Yield [%][b]	*ee* [%][c]
1	TESOH	THF	–	–	–
2	TMSOK	THF	–	–	–
3	TESOK	THF	3:1	39	96
4	TESOK	1,4-dioxane	4:1	n.d.	n.d.
5	TESOK	CH_2Cl_2	99:1	90	97
6	TMSOK	CH_2Cl_2	n.d.	30[d]	94
7	TBSOK	CH_2Cl_2	97:3	79	98
8	TIPSOK	CH_2Cl_2	86:14	64	99

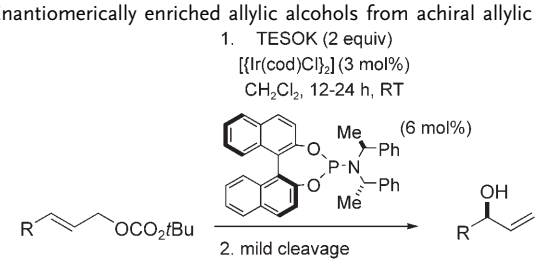
[a] Determined by ^{1}H NMR spectroscopy of the unpurified reaction mixtures. [b] Yield of the silyl ether after purification by chromatography. [c] The *ee* value was determined by HPLC on a chiral stationary phase (after deprotection using TBAF in THF). [d] The reaction was slow and did not reach completion. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, cod = cycloocta-l,5-diene, TBAF = tetra-*n*-butylammonium fluoride, n.d. = not determined.

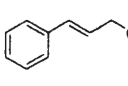
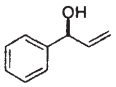
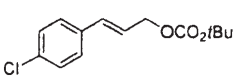
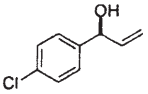
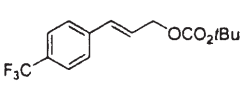
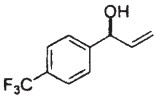
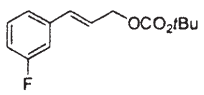
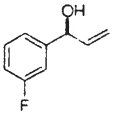
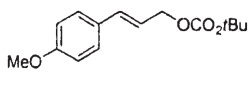
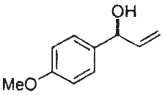
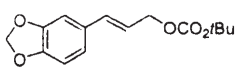
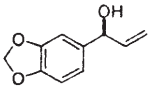
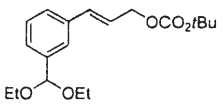
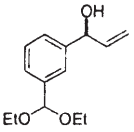
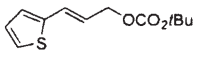
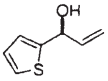
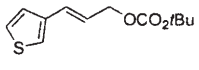
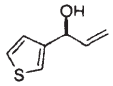
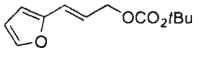
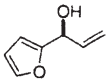
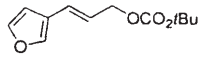
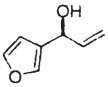
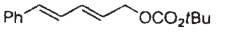
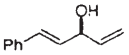
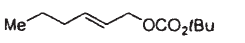
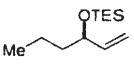
Gratifyingly, subsequent screening of reaction conditions showed that excellent results arose from changing the reaction solvent to CH_2Cl_2 (Table 1, entry 5). It is interesting that the Ir-catalyzed enantioselective allylations to date have been largely conducted in THF.[4–6] The pronounced solvent effect we observe may be relevant in other processes.[17]

In the context of our preliminary investigations, we noted that various silanolates could be utilized, including TBSOK and TIPSOK (Table 1, entries 7 and 8), with the products formed in 98 and 99% *ee*, respectively. Although the triisopropylsilanolate gave somewhat lower regioselectivity (**6**/**7** 86:14), the *tert*-butyldimethylsilanolate gave the ether **6** in high regioselectivity (**6**/**7** 97:3). The fact that both unhindered, labile (TES) as well as hindered, robust (TBS and TIPS) silyl ethers can be generated is significant. This conveniently permits access to free, optically active secondary alcohols (when using TES) as well as stable silyl ethers (TBS, TIPS) that can be carried through multistep reaction sequences.

Once the standard conditions were identified, our efforts focused on examining the range of substrates that would be tolerated (Table 2). Various electron-poor (Table 2, entries 2–

Table 2: Enantiomerically enriched allylic alcohols from achiral allylic carbonates.



Entry	Substrate	Product	Yield [%][a]	*ee* [%][e]
1			88[b]	97
2			74[b]	98
3			78[b]	98
4			64[c]	98
5			75[b]	95
6			72[b]	92
7			70[c]	98
8			62[b]	99
9			67[c]	98
10			50[c]	97
11			60[c]	99
12			65[b]	97
13			65[d]	95

[a] Yield after purification by chromatography; the regioselectivity was found to be >99:1 in favor of the branched product. [b] Silyl ether cleavage was carried out by using 30% aq NaOH in MeOH. [c] Cleavage of the silyl ether was carried out using TBAF. [d] Isolated as the silyl ether because of volatility problems of the corresponding alcohol. [e] The *ee* value was determined by HPLC or GC on chiral stationary phases; the absolute configuration was established as (*S*) for entry 1.

4) and electron-rich (Table 2, entries 5 and 6) aryl-substituted allylic carbonates can be used as the starting materials for the transformation. The subsequent cleavage of the silyl ether proceeds uneventfully to yield chiral alcohols in 64–88% yield and with 92–98% *ee*. Notably, the cleavage is conveniently carried out using TBAF in THF. However, a simple deprotection of the crude material with 30% aqueous NaOH in MeOH also allows straightforward access to chiral allylic alcohols. The process tolerates substrates with additional functional groups (for acetals, compare Table 2, entries 6 and 7) without showing any deleterious impact on the yield or enantioselectivity. Furthermore, the reaction can be carried out with heterocyclic-substituted allylic carbonates. Thus, thiophene- (Table 2, entries 8 and 9) and furan-substituted allylic alcohols (Table 2, entries 10 and 11) can be obtained in good yields and excellent enantioselectivities (97–99% *ee*). The reaction of a dienyl carbonate proceeds to give products with high regio- and enantioselectivity (Table 2, entry 12). The method is also tolerant of alkyl-substituted allylic carbonates (Table 2, entry 13).[18]

In conclusion, we have reported the first highly regio- and enantioselective Ir-catalyzed allylic etherification of a wide range of achiral allylic carbonates substituted with aryl and alkyl groups, by using potassium silanolates as the nucleophiles. Subsequent cleavage of the silyl ether of the TES adducts gives rapid and reliable access to chiral allylic alcohols in high yields and enantioselectivities. Stable silyl ethers (TBS, TIPS), which can be carried through multistep reaction sequences, can also be formed in excellent yields and enantioselectivities. The fact that optically active allylic alcohols are easily accessed with this methodology opens up new avenues for the synthesis of complex molecules by Ir catalysis. Additionally, the use of silanolates may be of interest in other carbon–oxygen bond-forming reactions. Further exploration of this methodology and its application in synthesis is underway, and will be reported in due course.

Experimental Section

Representative procedure: A Schlenk flask under argon was charged with $[\{Ir(cod)Cl\}_2]$ (10.1 mg, 15 μmol, 3 mol%) and (*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)bis[(1*S*)-1-phenylethyl]amine (Feringa phosphoramidite) (16.2 mg, 30 μmol, 6 mol%). THF (0.5 mL) and *n*-propylamine (0.5 mL) were added, and the reaction mixture was stirred at 50°C for 30 min. The solution was allowed to cool to RT and the volatiles were removed under high vacuum (30 min). A solution of potassium silanolate (1.00 mmol, 2 equiv) in CH_2Cl_2 (2 mL) was added, followed by *tert*-butyl carbonate (0.50 mmol, 1 equiv) in CH_2Cl_2 (2 mL), and the reaction mixture was stirred at RT. After completion of the reaction (usually 14 h), as determined by TLC, the crude mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude silyl ether. The ratio of regioisomers was determined by ^1H NMR analysis of the unpurified sample. The mixture was then dissolved in THF (5 mL), cooled to 0°C, and treated with TBAF (1M in THF, 1 mL, 2 equiv). The reaction mixture was stirred for 2 h, then partitioned between H_2O (50 mL) and CH_2Cl_2 (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude allylic alcohol. Purification of the residue by flash column chromatography on silica gel afforded the desired product.

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Keywords: alcohols · allylic compounds · asymmetric catalysis · iridium · nucleophilic substitution

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