Synthetic Methods

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The Enantioselective Allylation and Crotylation of Sterically Hindered and Functionalized Aryl Ketones: Convenient Access to Unusual Tertiary Carbinol Structures**

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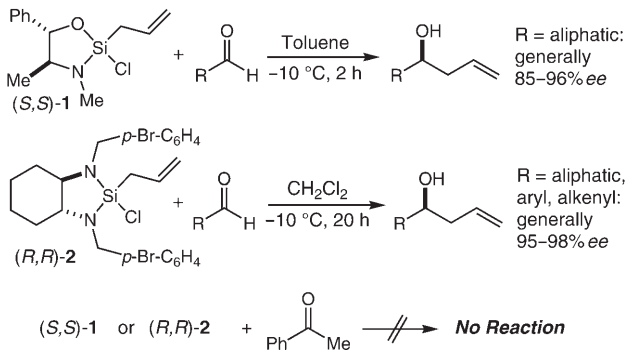
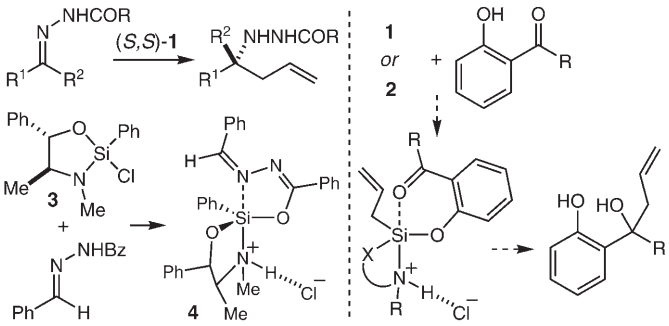
The development of reagents and catalysts for the enantioselective allylation of ketones has been an important goal in asymmetric synthesis for many years. Over the past decade, some important and seminal advances have been recorded, but most of these require the use of potentially toxic tin-based allyl reagents.[1] More recently, Chong,[2] Shibasaki,[3] Soderquist,[4] and Yamamoto[5] have recorded truly remarkable advances. With only a few notable exceptions, however, the scope of reactions that gives useful levels of efficiency and enantioselectivity remains limited to aryl methyl, cyclohexenyl methyl, and *tert*-butyl methyl ketones and structurally related derivatives thereof. There is no current solution at all for the enantioselective allylation of several important classes of ketones, including highly sterically hindered aryl alkyl ketones and diaryl ketones. In addition, only limited success has thus far been recorded in enantioselective ketone crotylation reactions, and no method that can produce both the *syn* and *anti* diastereomers with high levels of diastereo- and enantioselectivity has been reported. Our own recent investigations into the use of strained allylsilanes[6] for enantioselective aldehyde allylations and crotylations[7] prompted us to wonder whether these reagents might be rendered reactive enough for ketone allylation (Scheme 1). Preliminary experiments showed that with either reagent **1** or **2**, no reaction could be induced with acetophenone under a variety of conditions.



Scheme 1. Asymmetric aldehyde allylation.

Reagent **1** may also be employed for the enantioselective allylation of both aldehyde- and ketone-derived acylhydrazones (Scheme 2).[8] Mechanistic investigations showed that



Scheme 2. Proposed hydroxyketone allylation.

the reaction of phenylsilane **3** with the benzoylhydrazone of benzaldehyde gave **4**, as revealed by X-ray crystallography.[8b] Thus, it was discovered that these reactions proceed by covalent attachment of the acyl oxygen atom of the hydrazone to the allylsilane reagent by displacement of the chloride and that the liberated HCl protonates the amino group of the pseudo-ephedrine. The success of the hydrazone allylations may thus be attributed both to their intramolecular reaction pathway and to the presumably significant increase in Lewis acidity of the silane because of the protonation of the amino group. We reasoned that a suitable nucleophile (e.g., phenol) attached to the ketone substrates might mechanistically mimic the acylhydrazones, and therefore we set out to screen such hydroxyketones for reactivity with **1** and **2**.

2′-Hydroxyacetophenone was treated with both **1** and **2**. Although **1** failed to provide a clean reaction, **2** successfully

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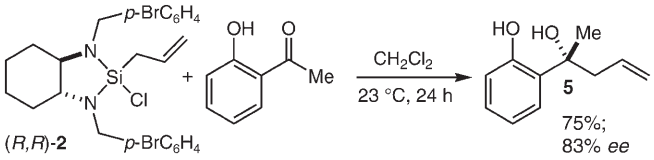
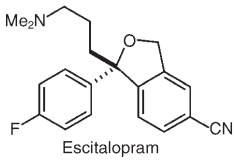
allylated the ketone to give tertiary carbinol **5** with encouraging levels of efficiency and enantioselectivity (Scheme 3). After optimization, the product could be obtained in 75% yield and 83% *ee*. Consistent with our mechanistic hypothesis, no allylation products were observed in the reactions of 3′- and 4′-hydroxyacetophenone with **2**. Although the poor performance of **1** is not well understood, we were nevertheless encouraged by the reaction of **2** with 2′-hydroxyacetophenone and undertook a survey of the reaction scope.



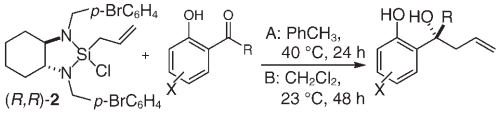
Scheme 3. Asymmetric ketone allylation.

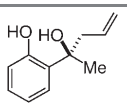
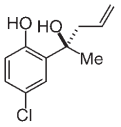
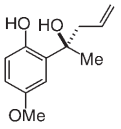
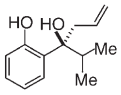
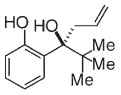
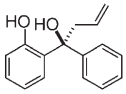
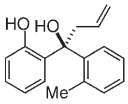
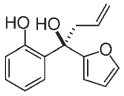
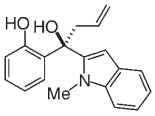
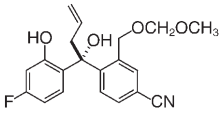
In the hydroxyacetophenone series, substitution of the phenol ring was tolerated with minimal impact on reaction performance (Table 1, entries 1–3). Remarkably, highly sterically hindered ketones could be tolerated as the isopropyl, and even the *tert*-butyl ketone, substrates were not only smoothly allylated but were allylated with improved enantioselectivity (entries 4 and 5). Aryl and heteroaryl ketones were also well tolerated (entries 6–10), thus providing access to enantiomerically enriched diaryl allyl tertiary carbinols. These products are particularly noteworthy in that they would likely be quite difficult to access by allylation of diaryl ketones without recourse to the directing-group strategy employed herein. Indeed, in all previous reports concerning enantioselective ketone allylation, no diaryl ketones have been reported as successful substrates. Thus, the method allows access to truly novel optically active tertiary carbinols, for which there is no obvious alternate approach. Escitalopram, the single enantiomer of the selective serotonin-reuptake inhibitor Celexa, makes the importance of diaryl carbinol derivatives of this type clear. A reasonable entry into systems such as these is demonstrated (entry 10) and further the tolerance of the reaction to extensive functionalization of the aryl rings is shown.



With only two limited exceptions,[3,5] the development of general enantioselective methods for ketone crotylation has proved elusive, and it was thus of interest to examine the corresponding *cis*- and *trans*-crotylsilanes in the present context. Previously reported *cis*-crotylsilane **6**[7c] was found to crotylate 2′-hydroxybenzophenone to give **7** in 63% yield and with excellent diastereo- and enantioselectivity (Scheme 4). The corresponding *trans* crotylsilane **8**[7c] provided **9** in 58% yield and with excellent diastereo- and enantioselectivity. These reactions represent the first method for the highly diastereo- and enantioselective synthesis of both the *syn*- and *anti*-crotyl diastereomers derived from ketones.

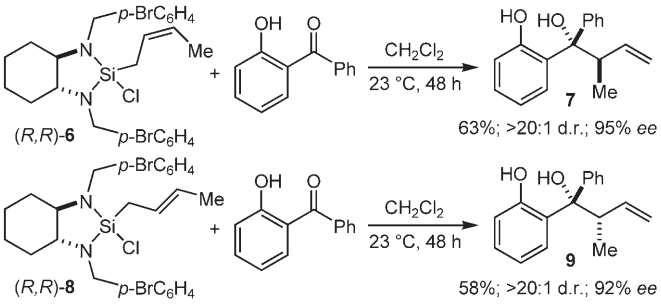
Table 1: Enantioselective allylation of 2′-hydroxyphenylketones.



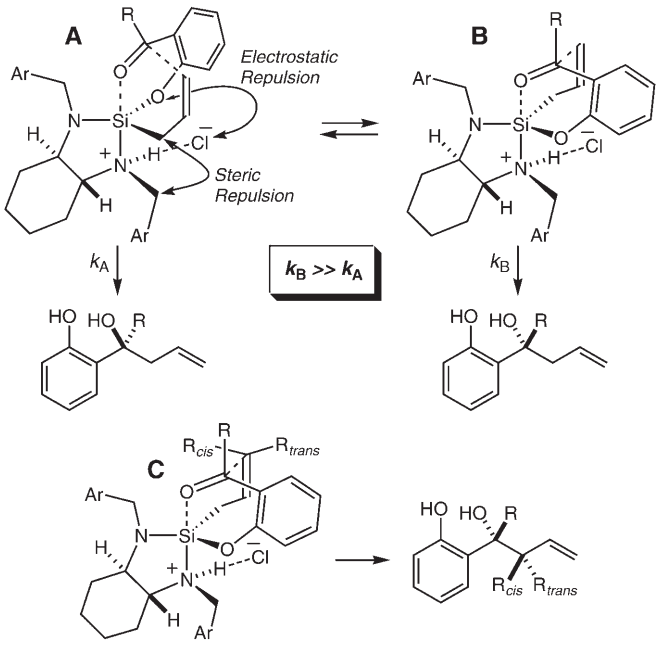
Entry	Conditions	Product	Yield [%]	*ee* [%]
1	A		75	83
2	A		65	81
3	A		64	82
4	A[a]		67	88
5	A[a]		63	93
6	B		62	93
7	B		75	94
8	B		76	88
9	B[a]		69	95
10	B[b]		90	90

[a] Reaction time = 48 h. [b] Reaction temperature = 0 °C.

In constructing a mechanistic and stereochemical model for these reactions, the following assumptions, based on the X-ray crystal structure of **4**, were made: 1) The phenol displaces the chloride from the silane, and HCl thus generated protonates one of the amino groups, and 2) the ketone oxygen atom and the protonated amino group occupy apical positions on the trigonal bipyramidal intermediate. Only two such intermediates are possible (**A** and **B**; Scheme 5). In **A**, the indicated steric and electrostatic interactions may plausibly be posited, whereas in **B**, which correctly predicts the observed major enantiomer, no such interactions are present. Further, it is noteworthy that the chairlike transition state depicted in **C** is consistent with the diastereoselectivity observed in the crotylation reactions described in Scheme 4.



Scheme 4. Enantioselective ketone crotylation.



Scheme 5. Mechanistic and stereochemical model.

A simple and convenient method for the enantioselective allylation and crotylation of hydroxyphenylketones has been described. An extraordinary and unprecedented degree of steric hindrance in the ketones is tolerated, and a wide variety of diaryl and heteroaryl ketones are excellent substrates as well, thus leading to structurally novel optically active tertiary carbinols that appear to be otherwise quite difficult to access. In addition, it is further remarkable that the same reagents that are effective for aldehydes are also effective for these ketone allylation and crotylation reactions, despite the fact that the aldehyde and ketone reactions are clearly mechanistically distinct processes. Current goals for this project include the extension of the method to additional classes of ketones and a more detailed understanding of the mechanism.

Experimental Section

General procedure for the enantioselective allylation and crotylation of 2′-hydroxyphenyl ketones: A round-bottomed flask was charged with reagent **2**, **6**, or **8** (1.5 mmol) and toluene or CH_2Cl_2 (5 mL; see Table 1 and Scheme 4). The desired 2′-hydroxyphenyl ketone (1.0 mmol) was then added (neat or as a solution in toluene or CH_2Cl_2 (1 mL)), and the resulting mixture was either cooled to 0 °C, left at ambient temperature, or heated to 40 °C (see Table 1 and Scheme 4). After 24 or 48 h (see Table 1 and Scheme 4), the reaction was quenched by the addition of methanol (3 mL). The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (10 mL). Water (5 mL) was added, and the layers were separated. The aqueous layer is extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography on silica gel yielded the pure tertiary homoallylic alcohol in the yields and stereoselectivities reported in Table 1 and Scheme 4. See the Supporting Information for full details.

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