COMMUNICATION

Diastereoselective allylation and crotylation of N-tert-butanesulfinyl imines with allylic alcohols†‡

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The palladium-catalyzed allylation of N-tert-butanesulfinyl imines with allylic alcohols in the presence of InI as reducing reagent takes place with high diastereoselectivity in reasonable yields. The reaction with crotyl alcohol is totally regioselective, leading to the anti-diastereomer as the main reaction product.

The stereoselective allylation of imines using organometallic compounds is of great interest in synthetic organic chemistry because the resulting homoallylic amines are valuable building blocks.[1] For instance, the double bond of the allylic moiety can participate in a number of further synthetically useful transformations: hydroboration, hydration, epoxidation, hydroformylation, ozonolysis, olefin metathesis, *etc.*[2] Among the stereoselective methodologies, the catalytic enantioselective allylations[3] rely on the use of chiral Lewis acids or chiral Lewis bases. In addition, double activation could be also achieved by using chiral bifunctional catalysts[4] by the simultaneous activation of both electrophilic and nucleophilic reaction partners through a cooperative action of different functionalities of the ligand. However, and in spite of the rapid evolution of catalytic methods in recent years, the use of stoichiometric reagents (including substrates and/or allylic organometallic partners) is still the favourite choice of organic chemists in the synthesis of key intermediates of natural products. In these diastereoselective allylations,[5] the stereochemical information can be transferred by substrate control, including chiral auxiliaries, or through the use of chiral reagents (reagent control). Sometimes a double induction could also be involved in the process, a match/mismatch effect being possible. Performing the

stereoselective allylation of imine derivatives with allylic halides in the presence of reducing metals under Barbier-type reaction conditions (metalation in the presence of the electrophile) is also of interest, because this strategy circumvents the need of isolating allyl metal species (the real nucleophiles), which usually are sensitive, and in many cases also toxic. The most commonly used metals in these transformations are chromium,[6] indium[7] and zinc.[8] Particularly noteworthy is the use of allylic alcohols as allylating reagents of carbonyl compounds and imines under palladium catalysis in the presence of a reducing reagent.[9] More recently, the use of the Kulinkovich reagent in the coupling of allylic alcohols with aldimines provides an alternative approach to regio-and stereodefined homo-allylic amines.[10] On the other hand, in the growing field of the synthetic applications of chiral N-tert-butanesulfinyl derivatives,[11] we reported the diastereoselective allylation[12] of N-tert-butanesulfinyl aldimines[13] and ketimines[14] with *in situ* generated allylindium reagents, and the first one-pot α-aminoallylation of aldehydes with chiral tert-butanesulfinamide, allylic bromides, and indium, which provides homoallylic amines with high chemo-and stereoselectivities.[15] The chiral auxiliary is easily accessible in both enantiomeric forms in large-scale processes[16] and can be easily removed under acidic conditions. Continuing our studies on the diastereoselective allylation of chiral sulfinyl imines, we report herein the use for the first time of allylic alcohols as allylating reagents of these chiral imines.

The chiral imine **1a** derived from (R)-tert-butanesulfinamide and 3-phenylpropanal was taken as the imine model for the optimization of the reaction conditions in the palladium catalyzed allylation with allylic alcohols and derivatives. Although many assays were undertaken, only the most significant ones are compiled in Table 1. Thus, the reaction of allyl alcohol (**2a**) with imine **1a** in the presence of InCl$_3$ (1 equiv.), In (2 equiv.) and a substoichiometric amount of Pd(PPh$_3$)$_4$ (5 mol%), in a 1:1 mixture of THF and water,[17] led to the expected reaction product **3a** (84%) along with the homoallylic alcohol **4** resulting from the allylation of the aldehyde after hydrolysis of the starting imine (Table 1, entry 1). However, the allylation with allyl acetate (**2b**) under the same reaction conditions gave alcohol **4** as the major reaction product and only a small

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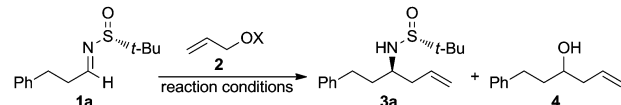E-mail: foubelo@ua.es, yus@ua.es

† This paper is dedicated to Professor Richard J. K. Taylor on occasion of his 65 birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures, full characterization, and copies of ¹H and ¹³C NMR spectra of compounds **3** and **6**. See DOI: 10.1039/c4cc02317j

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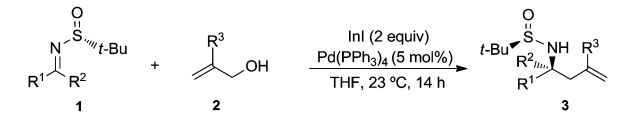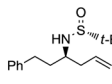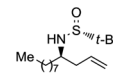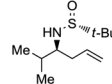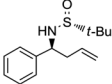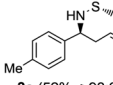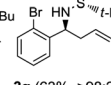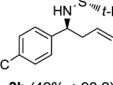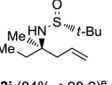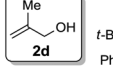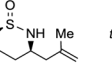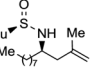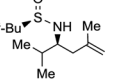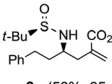
Table 1 Optimization of the reaction conditions[a]

		Products[b]
Entry	Reaction conditions	1a : 3a[c] : 4
1	**2a** (X = H, 1.0 mmol), In (0.4 mmol), InCl₃ (0.20 mmol), Pd(PPh₃)₄ (0.01 mmol), THF/H₂O (0.3 mL/0.3 mL), 23 °C (14 h)	0 : 84 : 16
2	**2b** (X = Ac, 1.0 mmol), In (0.4 mmol), InCl₃ (0.20 mmol), Pd(PPh₃)₄ (0.01 mmol), THF/H₂O (0.3 mL/0.3 mL), 23 °C (14 h)	0 : 12 : 88
3	**2b** (X = Ac, 0.8 mmol), In (0.4 mmol), InCl₃ (0.20 mmol), Pd(PPh₃)₄ (0.04 mmol), THF (1.0 mL), 23 °C (14 h)	92 : 8 : 0
4	**2c** (X = CO₂CH₂CH=CH₂, 0.8 mmol), In (0.4 mmol), InCl₃ (0.20 mmol), Pd(PPh₃)₄, (0.04 mmol), THF (1.0 mL), 23 °C (14 h)	75 : 15 : 10
5	**2b** (X = Ac, 0.8 mmol), In (0.4 mmol), InCl₃ (0.20 mmol), Pd(PPh₃)₄ (0.04 mmol), THF (1.0 mL), 60 °C (14 h)	0 : 95 : 5
6	**2a** (X = H, 0.8 mmol), InI (0.4 mmol), Pd(PPh₃)₄ (0.01 mmol), THF (1.0 mL), 23 °C (14 h)	0 : 100 : 0
7	**2b** (X = Ac, 0.8 mmol), InI (0.4 mmol), Pd(PPh₃)₄ (0.01 mmol), THF (1.0 mL), 23 °C (14 h)	0 : 79 : 21

[a] Reactions were carried out with 0.2 mmol of **1a**. [b] Ratio was determined from ¹H NMR spectrum of the crude reaction mixture. [c] Major diastereoisomer is shown.

amount of the desired homoallylamine derivative **3a** (Table 1, entry 2). It seems that allyl acetate (**2b**) is less reactive than allyl alcohol (**2a**) and hydrolysis occurred faster than allylation of the imine. On the other hand, the allylation with allyl acetate (**2b**) or diallyl carbonate (**2c**) proceeded very slowly when it was performed exclusively in THF at room temperature, and after 14 hours, 92 and 75%, respectively, of the starting material **1a** remained unreacted (Table 1, entries 3 and 4). Total conversion was observed when the allylation with allyl acetate (**2b**) was performed in THF at 60 °C, producing in this case **3a** and **4** in 95:5 ratio (Table 1, entry 5). Fortunately, we were please to find that switching from the combination In/InCl₃ to InI[18] as reducing reagent, the palladium catalyzed allylation of **1a** with allyl alcohol (**2a**) occurred with total conversion and selectivity at room temperature (Table 1, entry 6), meanwhile with allyl acetate (**2b**) an almost 4:1 mixture of the desired amine derivative **3a** and the homoallyl alcohol **4** was obtained (Table 1, entry 7). We studied next the scope of the allylation of N-tert-butylsulfinyl imines **1** with different allylic alcohols **2** by applying the optimized conditions depicted in Table 1, entry 6. The expected homoallylamine derivatives **3** were obtained in good yields for aliphatic aldimines and moderate-to-good yields in the case of aromatic aldimines using allyl (**2a**) and methallyl alcohol (**2d**) as allylating reagents (Table 2). It was also possible to carry out the allylation of the ketimine derived from butanone with allyl alcohol (**2a**) but under more demanding reaction conditions, 60 °C instead of room temperature in this case (Table 2, compound **3i**). Regarding aromatic imines, electron-rich derivatives seemed to perform better than the electron-poor ones (Table 2, compare compounds **3f** and **3h**). Interestingly, this methodology is compatible with both the use of functionalized allylic alcohols, such as ethyl 2-(hydroxymethyl)-acrylate (**2e**) (Table 2, compound **3n**), and the presence of an active sp² C–Br bond in palladium catalysis (Table 2, compound **3g**). On Table 2, yield and diastereomeric ratio for the allylation of chiral imine **1a** with allyl bromide in the presence of indium metal are also given in order to compare both methodologies. It could be said that palladium-catalyzed allylation of chiral imines **1** with allylic alcohols is superior to that using allylic halides taking into account stereoselectivities. Anyway, in both cases, they show the same sense of the stereochemical induction which is controlled by the configuration of the sulfur atom of the sulfinyl unit.

Table 2 Allylation of chiral imines **1**

[a] Major diastereoisomer is shown. [b] Yields were determined for isolated compounds after column chromatography. [c] Diastereomeric ratios were determined by ¹H NMR analysis of the crude reaction mixture. [d] For comparison, yield and dr reported for compound **3a** obtained by an indium mediated allylation with allyl bromide in THF at 60 °C.[13] [e] The reaction was performed at 60 °C.

The crotylation of chiral imines **1** was also investigated. The reaction of our imine model compound **1a** with crotyl alcohol (**2f**) under the standard conditions produced compound **3o** in a regioselective process with almost total face selectivity and low anti:syn diastereoselectivity (63:37), meanwhile the indium mediated crotylation of **1a** using crotyl bromide (**5**) occurred with high face-addition selectivity and a similar anti:syn ratio of 61:39 (Table 3). Surprisingly, the palladium-catalyzed crotylation of α-substituted (Table 3, compound **3p**) and aromatic imines occurred with high anti-diastereoselectivity in all cases (Table 3, compounds **3q–v**). On the other hand, the reaction of these aldimines with crotyl bromide (**5**)

Table 3 Crotylation of chiral imines **1**

a Major diastereoisomer is shown. *b* Yields were determined for isolated compounds after column chromatograph. *c* *anti* : *syn* ratios were determined by ¹H NMR analysis of the crude reaction mixture. *d* For comparison, yield and dr reported for compounds **3** obtained by an indium mediated allylation with crotyl bromide in THF at 60 °C.

proceeded also with better diastereoselectivities than for **1a**. A mechanism has been proposed for this palladium catalyzed allylations. First a π-allylpalladium complex **I** is formed. Indium salts facilitate the process by converting the hydroxy a better leaving group after coordination.[17] Then, the initially formed π-allylpalladium(ɪɪ) complex **I** is reductively transmetalated with indium(ɪ) salts to give allylindium(ɪɪɪ) species **II**, which is the real allylating reagent.[18] Face selectivity could be explained by considering six-membered cyclic transition states **III** (R² = H) or **IV** (R = Me) where the indium is coordinated to both the nitrogen and the oxygen atom of the sulfinyl imine, taking place a *Si*-face attack for imines with *R*-configuration at the sulfur atom. Regarding the regiochemistry and the diastereoselectivity in the crotylation reactions, the indium atom located at the terminal position in the allyl indium intermediate with *E*-configuration, the most stable carbanion, reacts at the γ-position through a cyclic boat-like six-membered transition state **IV** to produce the *anti*-isomer (Scheme 1). This kind of boat-like transition state **IV** has been proposed in a similar process to be preferred over

Scheme 1 Proposed reaction mechanism.
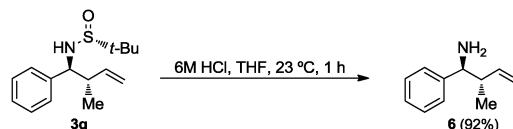
Scheme 2 Desulfinylation of **3q**.

the chair-like one **III** (in this case the *syn*-isomer would be produced), due to the steric repulsion between the methyl group and the substituent of the aldimine (Scheme 1).[19] Higher diastereoselectivities are obtained for the palladium-catalyzed allylations with alcohols when the processes are performed at room temperature, instead of 60 °C. On the other, and according with the proposed working model, the bulkier the substituent of the starting aldimine **1**, the higher diastereoselectivity is obtained (Table 3).

Finally, the *tert*-butanesulfinyl group was easily removed from compounds **3q** after treatment with a 6 M HCl aqueous solution in THF to give the known homoallylic amine **6**[20] with *anti*-relative configuration (Scheme 2).

In summary, allylation of *N-tert*-butanesulfinyl imines was performed with high diastereoselectivity with allylic alcohols under palladium-catalysis. The reaction with crotyl alcohol occurred also in reasonable yields and high *anti*-diastereoselectivity in a regioselective manner. In addition, and comparing to allylic halides, allylic alcohols are preferable allylating reagents by taking into account environmental (less toxic), economic (less expensive) and availability (numerous allylic alcohols are commercially available) considerations.

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