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Enantioselective rhodium(I)-triethylamine catalyzed addition of potassium isopropenyl trifluoroborate to enones

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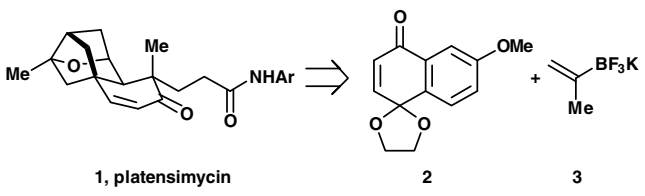
ABSTRACT

A general process is reported for the highly enantioselective 1,4-addition of isopropenyl trifluoroborate to cyclic enones under catalysis by a chiral Rh(I) complex and triethylamine at room temperature.

Recently, we reported a formal enantioselective synthesis of platensimycin (**1**),[1] in which the initial stereocenter was introduced by the catalytic enantioselective 1,4-addition of an isopropenyl group to enone **2** (Scheme 1). Despite the existence of numerous methods for enantioselective 1,4-addition to enones,[2–4] no instances of such reactions with secondary alkenyl groups had been described in the literature. We developed an approach that appears to be uniquely effective in achieving this transformation under special conditions with Rh(I) catalysis. The substrates used in this key step were **2** and **3**. In this Letter, we provide details of the discovery and the scope of this transformation.

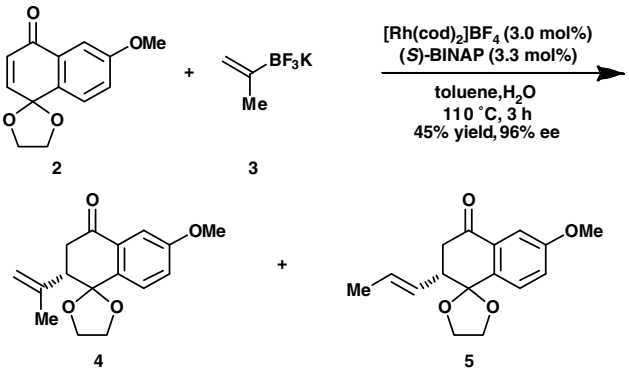
Our initial effort to achieve an enantioselective addition of potassium isopropenyl trifluoroborate to enone **2**, using standard reaction conditions,[5] resulted in the formation of a 1:1 mixture of addition products **4** and **5**, in only moderate yield because of concurrent hydrolysis of the ethylene ketal (Scheme 2). The enantiomeric purity of **4** was 96%. In order to suppress this hydrolysis, the 1,4-addition reaction was performed in the presence of triethylamine, which allowed the isolation of the same isomeric mixture of addition products in 95% yield.

An important finding from experiments using triethylamine as an additive was that this base not only inhibits Lewis acid-induced hydrolysis of the substrate, but also greatly accelerates the conjugate addition reaction. Consequently, higher temperatures are unnecessary and the reaction can be carried out at room temperature. Such mild conditions lead to a wider utility and greater efficiency of conjugate addition.



1, platensimycin 2 3

Scheme 1. 1,4-Addition as a key step in an enantioselective formal synthesis of platensimycin.



Scheme 2. Formation of the two isomeric products under standard reaction conditions.

At lower temperature the desired 2-propenyl adduct **4** is favored over the 1-propenyl adduct **5**. At 110 °C the products are formed in a 1:1 ratio, while at 80 °C **4** is favored by 1.2:1. At room temperature, **4** was formed as the *only product* of the reaction and was isolated in 96% yield and 94% ee. The exclusive formation of **4** at room temperature and the high enantioselectivity are noteworthy, especially since Genêt et al. have reported the formation of racemic products in all rhodium-catalyzed 1,4-additions of potassium trifluoroborates performed under 100 °C.[5]

Repeated experiments conducted without triethylamine confirmed that the amine base is responsible for *both* the reactivity and enantioselectivity observed in the reaction performed at room temperature.[6] Specifically, as summarized in Scheme 3, the conjugate addition reaction with **2** was not only slow at 23 °C in the absence of Et_3N (only 7% yield after 36 h), but also gave racemic product.

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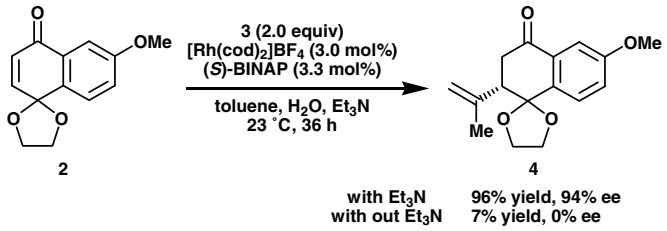
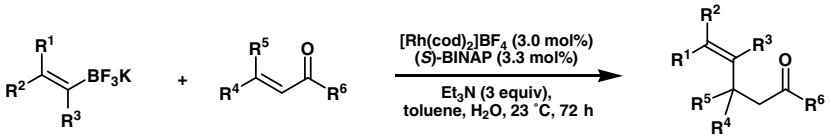


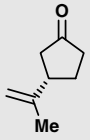
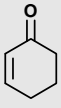
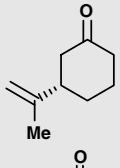
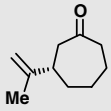
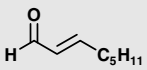
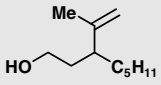
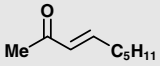
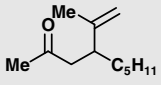
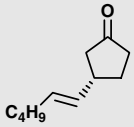
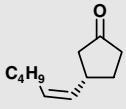
Scheme 3. The effect of triethylamine on the reactivity and selectivity of the 1,4-addition reaction.

Further optimization of the reaction parameters led to toluene and dioxane as optimal solvents for the reaction, whereas other common solvents, such as ether, dichloromethane, THF, and acetonitrile, led to significantly inferior yields and enantioselectivities. Of the common amine bases, triethylamine and Hünig's base were most effective, with the best results achieved in the presence of 2 equiv of triethylamine relative to the trifluoroborate salt. Under these optimized reaction conditions excellent yields and enantioselectivities were observed in reactions of potassium isopropenyl trifluoroborate with several cyclic enones (see Table 1, entries 1–3).[7,8] It is noteworthy that with an acyclic enone (entry 4) the conjugate adduct was formed in good yield, but was racemic. It was also possible to effect conjugate addition to the acyclic α,β-enal shown in entry 4 of Table 1, but here again the product was racemic. The addition of *Z* alkyl-substituted terminal alkenyl groups, which previously have not been used in enantioselective rhodium-catalyzed 1,4 addition reactions, was also achieved. The addition products of (*E*) and (*Z*)-1-hexenyl trifluoroborates and 2-cyclopenten-1-one were isolated in good yields and in 70% ee (entries 6 and 7).

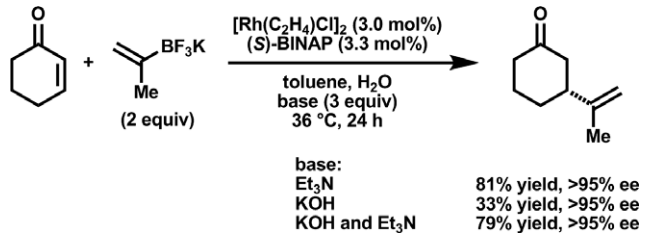
We performed several experiments aimed at understanding the underlying reasons for the beneficial effect of triethylamine on the conjugate addition process. When triethylamine was added to a solution of $[Rh(BINAP)Cl]_2$ and isopropenyl trifluoroborate in toluene-d_8-H_2O mixture, new signals in the ^{31}P NMR spectrum at 40.3 ppm (dd, J_{P-Rh} = 198 Hz, J_{P-P} = 30 Hz) and 44.4 ppm (dd, J_{P-Rh} = 194 Hz, J_{P-P} = 30 Hz) replaced the signals of the starting rhodium dimer within 10 min, indicating complete conversion of the dimer into transmetallation product [Rh(BINAP)(isopropenyl)L].

Table 1



Entry	Enone	Product	Yield (%)	$[\alpha]_D^{22}$ [a]	ee (%)
1			80	−112	93
2			87	−74	>98
3			89	−79	>98
4[b]			81	0	0
5			89	0	0
6[c]			89	−63	70
7[c]			83	−101	70

[a] c = 1 in $CHCl_3$.
[b] Alcohol isolated after $NaBH_4$ reduction of the crude product.
[c] Reaction time was 96 h.



Scheme 4.

Under the same conditions, in the absence of triethylamine, the formation of the transmetallation product was not observed even after 2 h. These experiments indicate that triethylamine accelerates the conjugate addition process by increasing the rate of the boron–rhodium transmetallation step.

One explanation for this dramatic effect could be that triethylamine facilitates the formation of rhodium hydroxo dimer. Hayashi et al. have reported that hydroxodimer, usually formed from $[Rh(BINAP)Cl]_2$ in the presence of KOH, readily participates in transmetallation reactions with boronic acids, and can serve as a superior catalyst for 1,4-addition of boronic acids.[9] In an attempt to observe the formation of the hydroxodimer, triethylamine was added to a solution of $[Rh(BINAP)Cl]_2$ in toluene-d_8–H_2O mixture. Over 4 h we observed a slow appearance of a new *singlet* in ^{31}P NMR at 27 ppm, indicating the loss of the original rhodium complex. However, when KOH or tetrabutylammonium hydroxide was used in place of Et_3N (conditions for formation of Rh-hydroxo dimer), the rate of the reaction was greatly decreased. (Scheme 4). When triethylamine was used in the reaction together with KOH, the rate of the reaction was not affected by the presence of KOH. The results of these experiments strongly suggest that hydroxide is not involved in the formation of the active catalyst.

An alternative explanation for the role of triethylamine, consistent with the results of our experiments, is the formation of a triethylamine rhodium complex, which serves as the active catalyst because it accelerates the B–Rh transmetallation reaction by displacement of the original ligand on Rh (X, e.g., X=OH). This would imply that the Et_3N ligand on Rh is more readily displaced than X^- (i.e., that Rh is more electrophilic with Et_3N as a ligand than with X^-).

In summary, we have described a highly efficient rhodium-catalyzed 1,4-addition of potassium vinyl trifluoroborate salts to cyclic enones in the presence of triethylamine. The low temperature at which reaction is conducted allows the use of vinyl trifluoroborate salts that are incompatible with the standard reaction conditions. Most notably, it allows accelerated enantioselective addition of an isopropenyl group to cyclic enones which could not be achieved using previously described procedures. We also provided evidence for the dramatic acceleration of the transmetallation step by Et_3N of the conjugate addition.

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6. The beneficial effect of triethylamine on the rate of rhodium catalyzed 1,4-additions to enones has been reported: Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000–6004.
7. To a 15 mL Schlenk tube were added $[Rh(cod)_2]BF_4$ (0.030 equiv, 0.015 mmol), (*S*)-BINAP (0.033 equiv, 0.016 mmol), and potassium vinyl trifluoroborate (2.00 equiv, 1.00 mmol). The Schlenk tube was flushed with nitrogen several times and degassed toluene (1.00 mL), triethylamine (3.00 equiv, 1.50 mmol), and water (0.50 mL) were added. After stirring the resulting mixture for 10 min at room temperature, freshly distilled enone (1.00 equiv, 0.50 mmol) was added. The Schlenk tube was closed and the reaction mixture was stirred at room temperature. After 72 h, the reaction mixture was diluted with CH_2Cl_2, transferred to a separatory funnel, and washed with 0.1 M aqueous HCl and brine. The organic fraction was dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography.
8. The absolute configuration of the products was assigned by analogy to the assignment made for compound **4**, which was elaborated into a product of a known absolute stereochemistry (see Ref. 1 for details).
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