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Synthesis of α-alkenyl-α-amino esters via addition of potassium Alkenyltrifluoroborate salts to imine in the presence of $Yb(OTf)_3$

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ABSTRACT

A simple protocol which led to an effective construction of α-alkenyl-α-amino esters was achieved under mild conditions. This transformation proceeded by Yb-catalyzed addition of alkenyltrifluoroborates across the imine double bond. A variety of functional groups could be applicable to both partners.

Introduction

β,γ-Unsaturated α-amino acid derivatives, a unique class of non-proteogenic amino acids, are the main structural motifs present in the realm of many biologically active natural compounds as well as pharmaceuticals.[1] The biological properties of certain amino acids and their derivatives are greatly affected by the presence of unsaturation in the side chain, which not only alters the metabolic activities of certain microorganisms, thus imparting potential therapeutic advantages, but also plays an important role in chemical transformation as well as chemical stapling.[2]

In the past decade, a great number of methods have been developed to access these valuable compounds.[1a] In contrast, from a synthetic standpoint, β,γ-alkenyl-α-amino acid derivatives are still challenging to make up. To date, only a few precedents are available.[3] However, to the best of our knowledge, approaches toward an important synthon for α-amino acids, β,γ-unsaturated α-amino acid derivatives, that explore the addition of potassium alkenyltrifluoroborate salts to α-imino esters catalyzed by ytterbium triflate are hitherto unprecedented.[4]

Potassium organotrifluoroborate salts have ousted their corresponding boronic acids because these air- and moisture-stable monomeric trifluoroborates can be easily prepared, have tremendous oxidative and thermal stability, and predictable reactivity patterns which ameliorates the yield of the desired products.[5]

In a previous attempt, a rhodium catalyst along with the ligand upon heating resulted in the formation of α-branched allylic amines.[3a,b] Herein, we would like to present a very simple reaction protocol which has not only eliminated the use of an expensive metal catalyst, but also eradicated the role of any ligand.[3a] Furthermore, our reaction proceeds under mild conditions for which the aid from a base, co-solvent, or heat is not required. Thus, it is worth studying ytterbium-catalyzed nucleophilic addition of potassium organotrifluoroborate to carbon heteroatom multiple bonds.

Results and discussion

We initiated our studies using PMP-protected α-imino esters, along with *trans*-styryltrifluoroborate, as they could be readily synthesized and are more stable than their corresponding imines. Furthermore, deprotection of the resulting products could be achieved under mild conditions using cerium ammonium nitrate (CAN).[6] In the absence of any catalyst, the reaction of potassium *trans*-styryltrifluoroborate with an α-imino ester did not deliver the desired product in reasonable yield (Table 1, entry1).

Then, we envisioned that the addition of potassium alkenyltrifluoroborate to α-imino esters using an appropriate metal activator should readily provide the α-alkenyl α-amino acid derivative (Table 1). By taking advantage of the numerous synthetic applications of Lewis acids, the robustness of this method was explored. We found that 10 mol % loading of Lewis acids, such as $Sc(OTf)_3$, $Cu(OTf)_2$, $Inbr_3$, $MnCl_2$, or AgOTf furnished the corresponding α-alkenyl-α-amino acid derivatives in CH_3NO_2 at ambient

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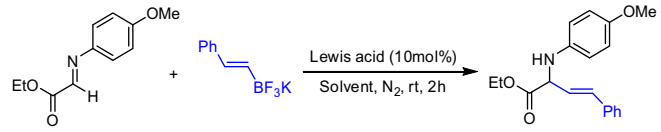
Table 1
Screening of Lewis acids for the addition of alkenyltrifluoroborate to α-imino esters



Entry	Catalyst	Base	Yield (%)
1	—	CH_3NO_2	<10
2	$Sc(OTf)_3$	CH_3NO_2	42
3	$Cu(OTf)_2$	CH_3NO_2	42
4	$InBr_3$	CH_3NO_2	41
5	$MnCl_2$	CH_3NO_2	18
6	AgOTf	CH_3NO_2	43
7	$Yb(OTf)_3$	CH_3NO_2	66
8	$Yb(OTf)_3$	CH_2Cl_2	70
9	$Yb(OTf)_3$	Dioxane	43
10	$Yb(OTf)_3$	THF	50
11	$Yb(OTf)_3$	CH_3CN	54
12	$Yb(OTf)_3$	MeOH	40

temperature in a period of 2 h, in 18–66% yield. Among them, $Yb(OTf)_3$ was found to be the most effective catalyst (Table 1, entry 7).

In continued pursuit of our goal to find the optimal reaction conditions, the screening of commonly used solvents with $Yb(OTf)_3$ revealed the suitability of this reaction with dichloromethane (Table 1, entry 8), which provided the best results in terms of yield.

After having optimized the reaction conditions in hand,[7] the general utility and scope of the reaction was explored. As summarized in Table 2, a variety of alkenyltrifluoroborates were successfully reacted with different α-imino esters, under same reaction conditions to afford the corresponding products with moderate to good yields.

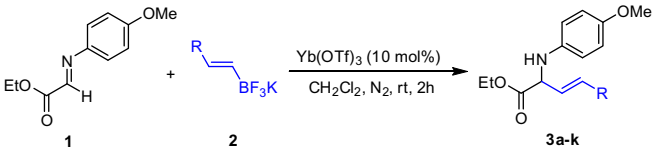
To verify the reactivity of different α-amino esters on the addition reaction of alkenylltrifluoroborate salts, a variety of imines (Table 3) were randomly chosen to prepare the corresponding amino esters under described reaction conditions.[7] In general, the addition reactions of alkenyltrifluoroborates with respect to the coupling partner highlighted that α-imino esters with an electron-donating group on the aromatic ring afforded the best results in terms of yield (Table 3, entries 1, 3 and 4), while α-imino esters with an electron-withdrawing substituent proved to be less reactive and resulted in low isolated yield (Table 3, entry 2).

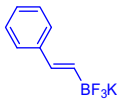
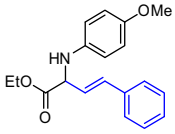
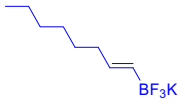
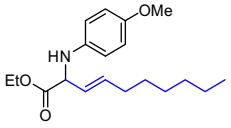
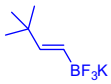
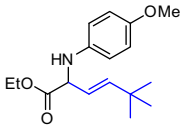
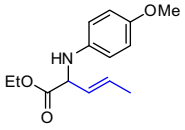
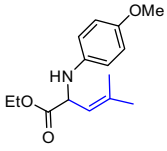
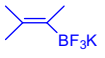
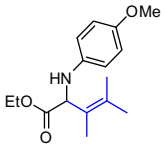
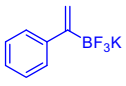
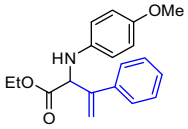
Real-time infrared techniques[8–10] were used to delve deeper into the reaction and provide a useful reaction outcome; the reaction between potassium *trans*-styryltrifluoroborate salts and ethyl 2-(4-methoxyphenylimino)acetate was chosen for this investigation. It was found that, after the addition of *trans*-styryltrifluoroborate, the characteristic band of imine at 1595 cm^{-1} slowly disappeared (see Supplementary data), indicating that the reaction had progressed to completion.

Initial mechanistic studies were undertaken to elucidate the details of the $Yb(OTf)_3$-mediated activation of α-imino esters. Matteson[11] and Kim demonstrated that Lewis acid activated alkenyltrifluoroborates to intermediate dihaloboranes, which is the active species in the reaction. In this way, a possible mechanism for this Yb(III)-catalyzed alkenylation is proposed in Figure 1.

In the first step, the electrophilic alkenyldifluoroborane generated in situ by the reaction between the corresponding alkenyltrifluoroborate salt **2** and the Lewis acid[11] forms a nitrogen-boron complex(I) with the α-imino ester. This complexation facilitates the migration of the alkenyl group from the boron to the C=N

Table 2
Addition of various alkenyltrifluoroborates to PMP-protected α-imino esters



#	Alkenyltrifluoroborate	Product	Yield (%)
1			70
2			43
3			54
4			21
5			82
6			72
7			0

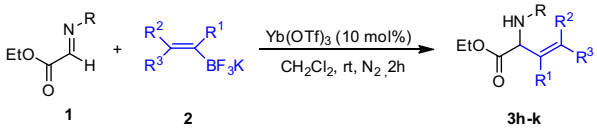
bond, forming intermediate(II). Finally, intermediate(II) is protonated by aqueous work-up, leading to the alkenyl amine and regenerating the active Yb(III) triflate.

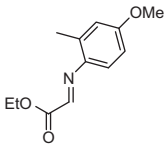
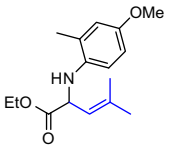
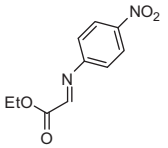
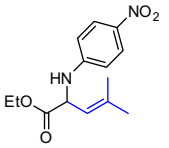
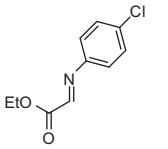
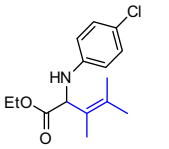
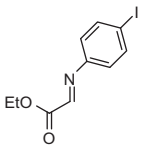
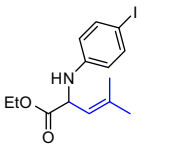
An interesting aspect of the use of rare earth metal triflates[12] is that the catalyst can be recovered from the reaction medium and recycled. This prompted us to evaluate the possibility of reusing $Yb(OTf)_3$ in our reactions. We were able to re-isolate the catalyst from the reaction medium by filtration, sequential washing with dichloromethane, and drying at 70 °C for 2 h. This process was repeated twice, affording the desired product in 82% (first run), 77% (second run), and 65% (third run) yield, as shown in Figure 2.

Conclusion

In conclusion, a particularly efficient and operationally trouble-free Lewis acid catalyzed α-imino ester C-alkenylation has been established. This method is worth considering as an unsaturation

Table 3
Addition of alkenyltrifluoroborates to various with α-imino esters



Entry	Alkenyltrifluoroborate	Imino ester	Product	Yield (%)
1				80
2				13
3				84
4				90

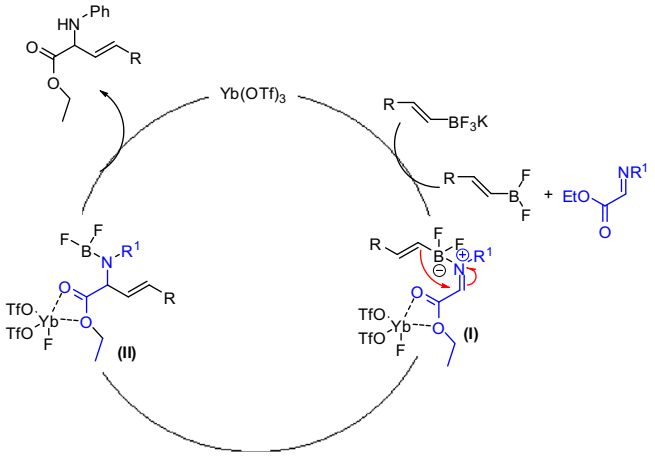


Figure 1. Proposed mechanism for the addition reaction of alkenyltrifluoroborates to α-imino esters.

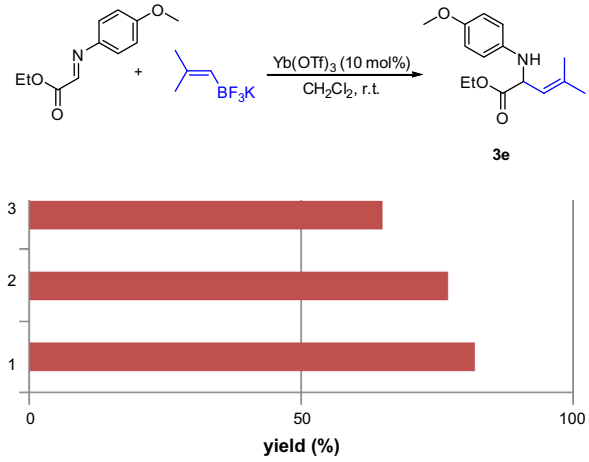


Figure 2. Recyclability of the catalyst.

since the product offers a versatile scaffold for further useful derivatization. It also provides the additional advantage of catalyst recovery.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.133.

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7. *General procedure:* To a solution of ethyl 2-[(4-methoxyphenyl)imino]acetate (0.5 mmol,) in CH_2Cl_2 (5 mL) in the presence of 10 mol % $Yb(OTf)_3$ catalyst was added potassium 2-methyl-1-propenyltrifluoroborate (0.6 mmol). The resulting solution was stirred at room temperature under a nitrogen atmosphere for 2 h. The reaction mixture was then filtered and washed with EtOAc, and the combined organic extract was concentrated under vacuum. All products were purified by silica gel column chromatography, eluting with hexane/EtOAc (9.5:0.5). *Ethyl 2-((4-methoxyphenyl)-4-methylpent-3-enoate (3e)* ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.9 Hz, 2H) 5.11 (d, J = 8.6 Hz, 1H), 4.66 (d, J = 8.6 Hz, 1H), 4.18–4.15 (m, 2H), 3.72 (s, 3H), 1.83 (s, 3H), 1.75(s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 152.6, 140.7, 138.6, 121.6, 115.1, 114.8, 61.1, 56.7, 55.7, 25.7, 18.7, 14.1; HRMS (m/z): $[MH]^+$calcd for $C_{15}H_{21}NO_3$: 264.1594, found: 264.1590.
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