Vanadium-Catalyzed C–C Coupling

Vanadium-Catalyzed *anti*-Selective Additions of Allenols to Imines**

Barry M. Trost and Catrin Jonasson*

The use of vanadium catalysis for organic reactions has been virtually limited to redox chemistry.[1] Only recently have a few reports of additions to carbonyl groups catalyzed by vanadium(IV) and (V) complexes appeared.[2] To our knowledge, the additions of nucleophiles to imines catalyzed by vanadium have not been recorded. Our recent interest in the in situ generation of vanadium enolates by isomerization of allenols led us to consider their ability to add to imines (see Scheme 1).[3] The importance of Mannich-type products with the juxtaposition of an α,β-unsaturated carbonyl group should make the products particularly useful synthetic building blocks.[4] Since protonation of the enolate[5] to form enone **E** (see Scheme 1) competes with the imine addition, the latter must be quite facile for success. The general poorer reactivity of imines compared to carbonyl groups with regard to nucleophilic addition bodes ill for a competition favoring addition over simple isomerization of the allenol. Despite this ominous precedent, we now report the successful realization of an atom-economic[6] addition of allenic alcohols and imines in an *anti*-selective fashion.

[*] Prof. B. M. Trost, C. Jonasson
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu

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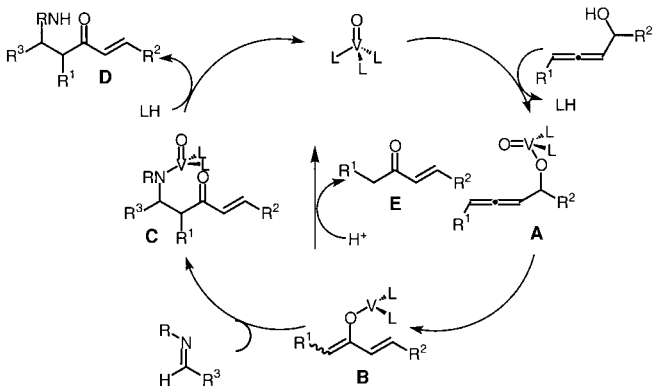
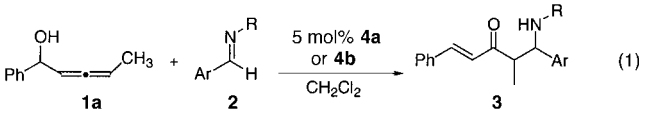


Scheme 1. Catalytic cycle. L = $OSiPh_3$.

To probe the feasibility of this process, the reaction in Equation (1) was used as the test[7] with $[VO(OSiPh_3)_3]$ (**4a**)[5c] as a catalyst. The results are summarized in Table 1.



(1)

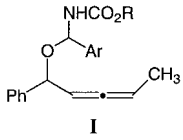
Interestingly, the simple Schiff base **2a** participates well in the reaction (entry 1). In contrast to our study of the reaction with aldehydes wherein *syn* diastereomers dominated, this reaction provided the *anti* diastereomers as the major product. Placing an electron-donating substituent in the *para* (entry 2) or *ortho* (entry 3) position of the *N*-aryl ring decreased the trapping dramatically. Thus, a removable electron-withdrawing substituent was placed on the nitrogen center. The *N*-sulfonyl analogue **2d**[8] was a poor participant (entry 4). The low yield of the adduct **3d** was mainly due to the inefficiency of trapping since the simple rearranged enone was the major product.

Table 1: Selected optimization data for **2**; Ar = Ph.[a]

Entry	R	Imine **2**	Product **3**	Yield [%][b]	*anti*/*syn*[c]
1	Ph	**2a**[d]	**3a**	91	1.7
2	$C_2H_4OCH_3$-4	**2b**[d]	**3b**	43	1.3
3	$C_6H_4CH_3$-2	**2c**[d]	**3c**	< 20	1.8
4	$PhSO_2$	**2d**[d]	**3d**	22	0.2
5	CH_3OCO	**2e**[d]	**3e**	22	9.0
6	CH_3OCO	**2e**[d]	**3e**	67	9.0
7	CH_3OCO	**2e**[e]	**3e**	72	9.0
8	CH_3OCO	**2e**[e]	**3e**	85	9.0
9	C_2H_5OCO	**2f**[e]	**3f**	67	7.3
10	*i*-C_3H_7OCO	**2g**[e]	**3g**	86	7.3

[a] In a typical procedure, the reactions were performed at substrate concentrations of 2.5 M with 5 mol% of catalyst **4a** under an argon atmosphere; entries 1–5 were run at room temperature, entries 6 and 7 at 35 °C with an addition time of 10 h for imine, and entries 8–10 at 35 °C with an addition time of 20 h. Reactions with addition times of 10 h and 20 h were performed by using a syringe pump. [b] Yield of isolated product after flash chromatography. [c] Determined by ^1H NMR spectroscopy and HPLC. [d] In this run, 1.2 equivalents of imine were employed. [e] In this run, 1.05 equivalents of imine were employed.

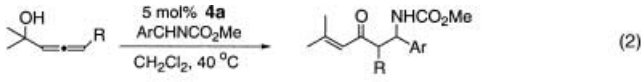
Replacing the poorly Lewis basic sulfone **2d** by the more Lewis basic carbamate **2e**[9] increased the diastereoselectivity dramatically. Surprisingly, the initial reaction still showed a poor yield of adduct **3e** (entry 5); however, for a different reason. Instead of untrapped rearranged ketone, the major product was the aminal **I** (R = CH_3, C_2H_5, *i*-C_3H_7) derived from simple addition of the alcohol to the imine. Remarkably, this adduct forms irreversibly in the presence or even absence of the vanadium catalyst. A dramatic improvement of the yield (entry 6) occurred when the allenic alcohol was added over a period of 10 h at 35 °C. A combination of lowering of the amount of imine from 1.2 equivalents to 1.05 equivalents (entry 7) together with increasing the time over which the addition was made, led to high yield and diastereoselectivity (entry 8). No advantage accrues from changing the methyl group to an ethyl (entry 9) or isopropyl group (entry 10). Switching solvents (toluene, dichloroethane, THF, 1,2-dimethoxyethane, and acetonitrile) had no beneficial effects.



I

Adopting the conditions of entry 8, Table 1, as our standard, the variation of the imines was explored (see Table 2). Use of imines bearing electron-withdrawing substituents proved more problematic. The difficulty derives from the ease of formation of the simple addition product of the alcohol to the imine. Thus, the *p*-chloro substrate **2l** gave less than 20% yield of the adduct **3l** under normal conditions. Increasing the temperature to 40 or 45 °C improved the yield to 55–58%. Using a more active catalyst $[VO(OSi(p\text{-}ClC_6H_4)_3)_3]$ (**4b**) further increased the yield to 69%. With the more strongly electron-withdrawing nitro group, as in imine **2m**, the yield with this more reactive catalyst was still only 40%. Satisfactory diastereoselectivities were obtained in these latter two cases. Aliphatic imines such as that derived from pivaldehyde failed to react. The monosubstituted allenic alcohol **1b** participates well in the reaction to give adduct **6** (Table 2 entry 8).

Nonaromatic allenic alcohols are suitable substrates for the reaction as shown in Equation (2). With the parent imine, good yield and excellent diastereoselectivity of adduct **5a** was

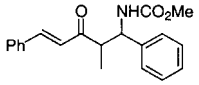
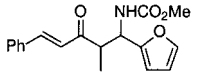
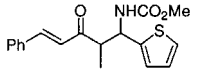
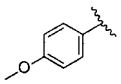
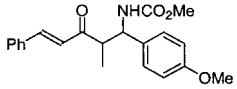
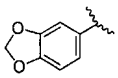
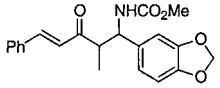
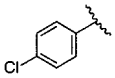
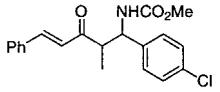
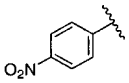
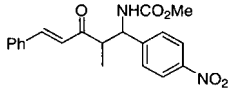
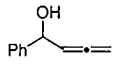
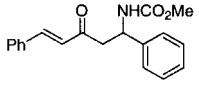


(2)

1c: R=CH_3 — **5a**: R=CH_3, Ar=Ph, 70%, *anti*/*syn*=32.3
1c: R=CH_3 — **5b**: R=CH_3, Ar=2-thienyl, 82%, *anti*/*syn*=4.9
1d: R=*n*-C_5H_{11} — **5c**: R=*n*-C_5H_{11}, Ar=Ph, 86%, *anti*/*syn*=24
1e: R=*i*-C_3H_7 — **5d**: R=*i*-C_3H_7, Ar=Ph, 66%, *anti*/*syn*=1.9

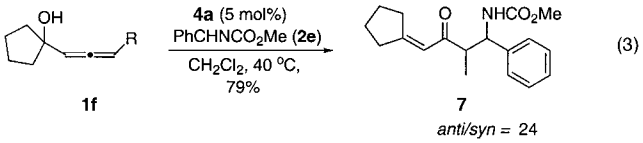
obtained. Better yields were obtained for the 2-thienyl derivative **5b**. While the diastereomeric ratio (d.r.) of **5b** decreased from that of **5a**, it was higher than that observed with allene **1a** (Table 2, entry 3). Increasing the chain length, for example **1d**, also gave excellent results [Eq. (2)]. On the other hand, the branched isopropyl-substituted substrate **1e** gave a diminished d.r. Increasing the size of the substituents at the alcohol center as in **1f** still gave excellent results [Eq. (3)].

Table 2: Vanadium-catalyzed additions of allenic alcohols and *N*-methoxycarbonyl (*N*-Moc) imines.[a]

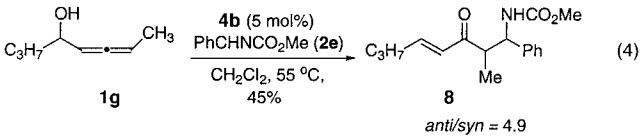
Entry	Allenic alcohol	2	Ar	Product	Yield [%][b]	*anti/syn*[c]
1	**1a**	**2e**	Ph		**3e** 85	9.0
2	**1a**	**2h**			**3h** 80	4.3
3	**1a**	**2i**			**3i** 81	3.2
4	**1a**	**2j**			**3j** 82	1.6
5	**1a**	**2k**			**3k** 79	1.5
6	**1a**	**2l**			**3l** 69[d]	6.1
7	**1a**	**2m**			**3m** 40[d]	6.1
8		**2e**	Ph		**6** 78	NA[e]

[a] In a typical procedure the reactions were carried out at 35–45 °C in dichloromethane (2.5 M) by employing 5 mol% [VO(OSiPh$_3$)$_3$] (**4a**) and 1.05 equivalents of *N*-Moc imine, under an atmospheric pressure of argon. The allenic alcohol (1.0 equiv) was added slowly over 20 h. [b] Yield of isolated product after flash chromatography. [c] The *anti/syn* ratio was determined by ^{1}H NMR spectroscopy and HPLC. [d] [VO(OSi(*p*-ClC$_6$H$_4$)$_3$)$_3$] (**4b**) was used as the catalyst (5 mol%). [e] NA = not applicable.

Using an allenic alcohol bearing only a single alkyl substituent at the carbinol carbon atom as in **1g** led to a slower reaction [Eq. (4)] and thus required use of the more active chloro-substituted catalyst **4b**.



(3)



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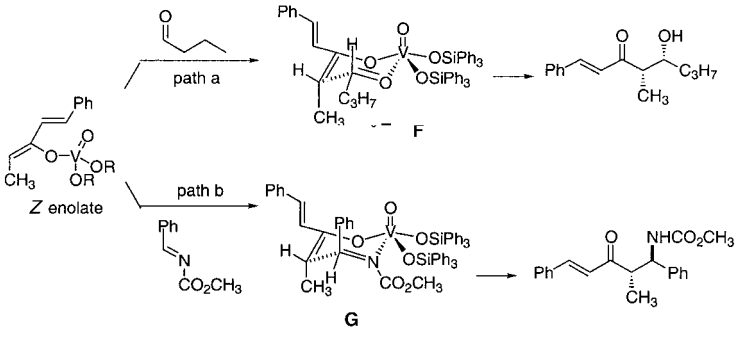

(5)

The assignment of the major diastereomer as *anti* is based upon an X-ray crystallographic analysis of adduct **7** and correlations of ^{1}H and ^{13}C NMR data as detailed in the Supporting Information. The current report describes an atom-economical method for the stereoselective synthesis of products possessing simultaneously, an α,β-unsaturated ketone and a β-amino ketone that cannot be easily obtained by alternative means. To our knowledge, this is the first report involving the additions of vanadium enolates to imines. Whereas additions of these enolates to aldehydes preferably generate the *syn* adducts, the addition to imines generates the *anti* adducts. This complementary behavior can be rationalized by the [3.3] sigmatropic rearrangement of **A** (Scheme 1) preferentially forming the *Z* enolate. As shown in path a of Equation (5), coordination of the least hindered lone pair in the case of the aldehyde then leads to the *syn* adduct **F**, whereas, similar coordination to the single lone pair of the *E* aldimine must lead to the *anti* adduct **G**. It appears that vanadium enolates may prove to be generally useful in additions to all types of π-unsaturated systems. Their ease of generation by [3.3] sigmatropic rearrangements of propargyl and allenyl alchohols offers a novel new strategy for the synthesis of versatile building blocks.

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Keywords: allenols · asymmetric catalysis · atom economy · imines · sigmatropic rearrangement · vanadium

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