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Catalytic Conjugate Additions of Nitrogen-, Phosphorus-, and Carbon-Containing Nucleophiles by Amphoteric Vanadyl Triflate

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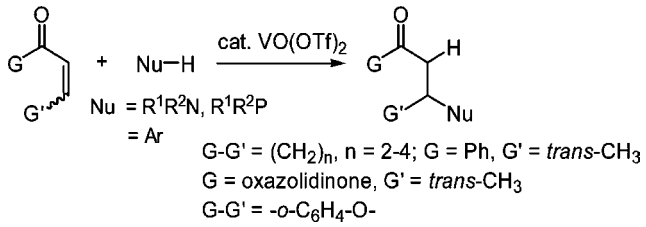
ABSTRACT



A series of carbamates, amides, *N*-tosyl amides, (hetero)arenes, and hydrogen phosphines/phosphites has been examined as nucleophiles for (hetero)Michael-type additions to enones and enamides catalyzed by amphoteric vanadyl triflate under mild and neutral conditions. The newly developed C–N, C–P, and C–C bond-formation protocols were carried out smoothly in good to high yields without intervention of any 1,2-additions.

Conjugate addition to α,β-unsaturated carbonyl compounds (i.e., Michael addition) is one of the most important carbon−carbon and carbon−heteroatom bond-forming strategies for synthetic organic chemistry.[1] Common conjugate addition reactions involve the addition of a protic nucleophile donor (e.g., C, Si, Sn, N, P, O, S, Se, I, or H) to an alkene or alkyne acceptor which is activated by an electron-withdrawing group (e.g., ketone, ester, amide, nitrile, nitro, sulfonate, and phosphonate). Subsequently, the resulting incipient enolate is trapped with a proton source. Besides conventional conjugate additions in basic media, a myriad array of metal-centered Lewis acid catalysts has been developed in view of the tremendous needs in asymmetric synthesis toward natural products and chiral drugs.[2] Metal salts or complexes derived from Al(III),[3] In(III),[4] Bi(III),[5] Re(V),[6] Fe(III),[6,7] Ru(III),[6,8] Rh(III),[6,9] Ir(III),[10] Ni(II),[11] Pd(II),[6,12] Pt(IV),[6] Cu(II),[13] and Au(I/III)[6] are the most extensively explored. However, only a couple of these catalysts can be applied to three different types of nucleophiles. Very recently, a strong Brønsted acid Tf_2NH was found to be capable of catalyzing

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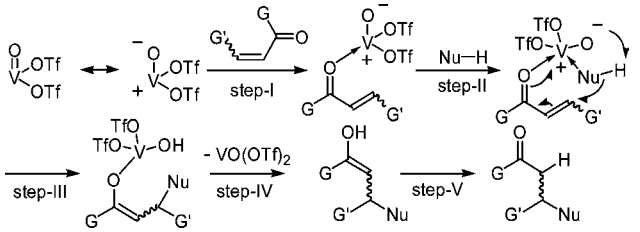
more than three different Michael additions specifically to acyclic α,β-unsaturated carbonyl compounds.[14] Therefore, a milder Lewis acid catalyst that can tolerate more nucleophile classes for functionalized Michael acceptors remains to be explored.

As part of our ongoing programs on the uses of vanadyl and oxometallic species in catalyzing C−X bond formation,[15a,b] asymmetric aerobic oxidation[15c,d] and oxidative coupling,[15e] and DNA photocleavage,[15f] we sought to evaluate the feasibility of catalyzing the conjugate addition event by using amphoteric vanadyl triflate. Namely, the partial positively charged V in V═O is Lewis acidic enough to first activate an electrophile (i.e., Michael acceptor) (Scheme 1, step-I).

Scheme 1. Postulated Mechanism for Amphoteric Vanadyl Triflate Catalyzed Conjugate Addition



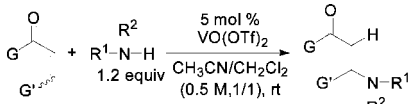
Conversely, the partial negatively charged O in V═O serves as a Lewis base to promote a subsequent proton transfer (step-II and step-III) of a coordinated protic nucleophile (i.e., Michael donor) during the addition event. Under such circumstances, the mediated reaction can proceed in a sequential push−pull-type mechanism toward the substrate pairs (Scheme 1).

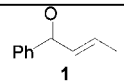
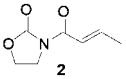
Herein we disclose our preliminary finding toward this end. To the best of our knowledge, this is the first successful demonstration of conjugate additions to α,β-unsaturated carbonyl compounds by group V (i.e., nitrogen and phosphorus) and carbon nucleophiles catalyzed by an oxometallic species—vanadyl triflate.

Carbonyl compounds bearing β-amino and -amido as well as their downstream derivatives such as β-lactams and 1,3-amino alcohols are versatile precursors of many biologically active natural products.[16] Although the carbon−carbon bond formation between enolates and imines (Mannich-type reaction) is a powerful means for constructing this functional subunit, the conjugate additions of amine equivalents to α,β-unsaturated carbonyls (i.e., aza-Michael addition) constitute another direct and efficient methodological strategy. Notably, catalytic activation of weaker nitrogen-centered nucleophiles such as carbamates proves to be more difficult and can be realized only very recently by the use of some delicately designed Brønsted[14] and Lewis acids (e.g., Bi(III),[5a] Re(V),[6] Ir(IV),[6] Pd(II),[12b] Pt(IV),[6] Fe(III),[7] Cu(II),[13a] and Au(I)[6]).

But-2-enoylbenzene **1** was first chosen as a test Michael acceptor, and $EtOC(O)NH_2$ (1.2 equiv) was used as a test carbamate-type Michael donor in the presence of catalytic $VO(OTf)_2$ in various solvent systems.[17] It was found that the conjugate addition proceeded smoothly by using 5 mol % of $VO(OTf)_2$ in 0.5 M CH_3CN/CH_2Cl_2 (1/1) at ambient temperature (entry 1, Table 1).

Table 1. Aza-Michael Additions Catalyzed by $VO(OTf)_2$



entry	Michael acceptor	R^1R^2N-H	time, h	yield,[a] %
1	 **1**	$EtOC(O)NH_2$	23	94 (**1a'**)
2	**1**		28	90 (**1b'**)
3	**1**	$PhC(O)NH_2$[b]	21	76 (**1c'**)
4	**1**	4-$MeC_6H_4SO_2NH_2$[c]	109	88 (**1d'**)
5	 **2**	4-$MeC_6H_4SO_2NH_2$[d]	384	58 (**2a'**)
6	2-cyclohexenone (**3**)	$PhCH_2OC(O)NH_2$	32	82 (**3a'**)
7	**3**		40	85 (**3b'**)
8	**3**	$PhC(O)NH_2$[b]	41	74 (**3c'**)
9	**3**	4-$MeC_6H_4SO_2NH_2$[c]	144	60 (**3d'**)
10	2-cyclopentenone (**4**)	$PhC(O)NH_2$[b]	38	63 (**4a'**)
11	2-cycloheptenone (**5**)	4-$MeC_6H_4SO_2NH_2$[c]	134	74 (**5a'**)

[a] Isolated, purified yield. [b] Performed in neat benzamide at 70 °C with 1.5 equiv of enone. [c] 2.0 M in CH_3CN/CH_2Cl_2 (1/1). [d] 2.0 M at 40 °C with 10 mol % of $VO(OTf)_2$ and 2.0 equiv of *p*-$TsNH_2$.

With the preliminary success, aza-Michael additions to other Michael acceptor classes like *N*-but-2-enoyl-1,3,2-oxazolidinone **2** and 2-cycloalkenones **3**−**5** by three different N-centered weak nucleophiles including carbamates, benzamide, and *p*-toluenesulfonamide (*p*-$TsNH_2$) were further explored (Table 1). It was found that all the catalytic reactions, except the benzamide additions and the addition

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(17) (a) Among 14 different oxometallic species, only MoO_2Cl_2 and $VO(OTf)_2$ show promising catalytic efficiency. (b) For X-ray crystal structure of $VO(OTf)_2 \cdot 5H_2O$, see: Magnussen, M.; Brock-Nannestad, T.; Bendix, J. *Acta Crystallogr., Sec. C* **2007**, *63*, m51.

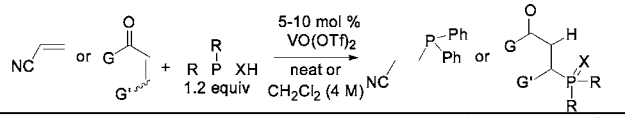
of *p*-$TsNH_2$ to the least reactive substrate **2**, proceeded smoothly under the optimal reaction conditions. In general, the carbamates such as $EtOC(O)NH_2$, $BnOC(O)NH_2$, and 1,3-oxazolidin-2-one are the most reactive Michael donors. The conjugate additions were complete in 23−40 h with 82−94% isolated yields for enone substrates **1** and **3** (entries 1, 2, 6, and 7). In the case of benzamide addition, the reactions required heating at 70 °C.[18] Under such circumstances, the Michael reactions went to completion in 21−41 h with 63−76% yields (entries 3, 8, and 10). Notably, the current results are somewhat comparable to $Pd(PhCN)_2Cl_2$-catalyzed additions to unsaturated olefins, which was the most effective catalytic system reported previously.[12c]

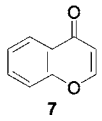
Furthermore, *p*-$TsNH_2$ is amenable to the catalytic conjugate addition with enones as represented in **1**, **3**, and **5** (Table 1). All the reactions proceeded reasonably well in 60−88% yields, albeit with a prolonged reaction time (109−144 h; entries 4, 9, and 11 in Table 1). In comparison, these cases are superior to the literature results of accessing **1d′** and **3d′** in 40 and 17% yields, respectively, in two steps.[19] Notably, these two examples of direct aza-Michael additions to access the desired products have never been documented. The current catalytic protocol offers a handy, one-step procedure to synthesize these target adducts in satisfactory yields.

Chiral organophosphorus compounds are valuable ligands for transition metal complexes as asymmetric catalysts for enantioselective transformations.[2a] Dialkylphosphites are versatile phosphorylation reagents to aldehydes (i.e., Pudovik reaction), ketones (i.e., Abramov reaction), and the corresponding α,*β*-unsaturated carbonyls. The resultant α-hydroxy- and *γ*-oxo-phosphonates are useful synthetic intermediates. Conventionally, these reactions were performed under basic or neutral conditions at elevated temperature. In recent years, the analogous catalytic variants for their additions to α,*β*-unsaturated carbonyls by the action of Lewis acids have been developed with significant success.[20] In marked contrast, the uses of hydrogen phosphines (R_2PH) for similar transformations pose a more difficult challenge and were relatively unexplored.

In view of the preliminary success on the catalytic conjugate additions to α,*β*-unsaturated carbonyls by weak N-centered protic nucleophiles, we further investigated the corresponding phospha-Michael additions by using Ph_2PH and $(RO)_2POH$ in the presence of catalytic $VO(OTf)_2$. It was found that the conjugate additions of Ph_2PH to acrylonitrile **6** (5 equiv) and 2-cyclohexenone **3** (2 equiv) proceeded smoothly in 21−32 h with 10 mol % of $VO(OTf)_2$ at ambient temperature, leading to **6a′** and **3e′** in 80 and 84% yields, respectively (Table 2). In the latter case, the product **3e′** was

Table 2. Phospha-Michael Additions Catalyzed by $VO(OTf)_2$



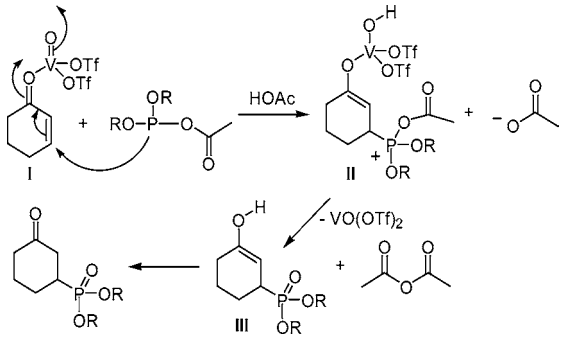
entry	Michael acceptor	R_2P-XH	time, h	yield,[a] %
1	$NCCH{=}CH_2$ (**6**)[b]	Ph_2P-H	32	80 (**6a'**)
2	**3**[c]	Ph_2P-H	21	84 (**3e'**)
3[d]	**3**	$(PhCH_2O)_2P$-OH	5	75 (**3f'**)
4[e]	 **7**	$(CH_3CH_2O)_2P$-OH	22	86 (**7a'**)

[a] Isolated, purified yield. [b] 5 equiv of acrylonitrile **6** was used. [c] 2 equiv of **3** was used. [d] Ac_2O (1.3 equiv) was added. [e] Carried out at 70 °C.

isolated as the corresponding phosphine oxide during column chromatography without exclusion of oxygen.

In marked contrast, no reactions were observed for $(PhCH_2O)_2POH$ under the same catalytic conditions. Since a more reactive hydrogen phosphite [$(RO)_2POH$; P(III)] tends to equilibrate favorably to its less reactive hydrogen phosphonate [(RO)P(O)H; P(V)],[20a,c] we sought to improve its nucleophilicity by treatment with Ac_2O in the presence of $VO(OTf)_2$. Under such circumstances, both forms can be converted to the corresponding acetylphosphite ($AcOP(OR)_2$) by catalytic nucleophilic acyl substitution (NAS, Scheme 2)

Scheme 2. Proposed Mechanism for Phospha-Michael Addition of an Acetylphosphite to an Enone Catalyzed by $VO(OTf)_2$



reaction, which is similar to the NAS of Ac_2O by alcohols.[15a]

With the in situ generated acetylphosphite (e.g., $(BnO)_2$-POAc), the corresponding phospha-Michael addition to 2-cyclohexenone **3** can be facilitated by 5 mol % of $VO(OTf)_2$ at ambient temperature in neat medium, leading to the adduct **3f′** in 75% yield in 5 h (entry 3). Notably, the acetylphosphite serves as a better alternative to the corresponding silylphosphite ($(RO)_2POSiR'_3$)[20b,21] for the conju-

(18) The chemical yields are around 34∼50% when the reactions were performed at ambient temperature in neat benzamide.

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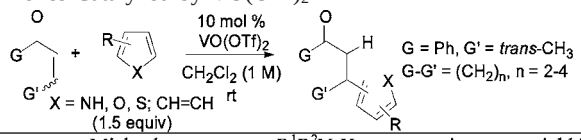
gate additions mediated by Lewis acids since its in situ generation and subsequent conjugate addition can be carried out in one pot by using our new catalytic protocol. Furthermore, a very sluggish Michael acceptor, flavone **7**, can also be utilized for the conjugate addition by ethylphosphite ($(EtO)_2POH$). Under the same catalytic conditions at 70 °C, the addition was complete in 22 h and the product **7a′** was isolated in 86% yield (entry 4). Notably, in all of the cases in Tables 1 and 2, except the conjugate additions of benzamide to 2-cycloalkenones,[22] no discernible product was observed in the absence of vanadyl triflate under the same reaction conditions.

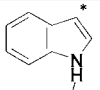
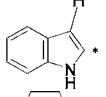
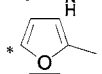
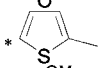
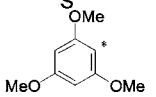
The working mechanism for the phospha-Michael addition is believed to proceed through initial activation of an enone by $VO(OTf)_2$. The acetylphosphite adds to the activated enone **I** in a 1,4-fashion to generate a protonated vanadyl enolate **II** by acetic acid produced in the initial acetylation of hydrogen phosphite (Scheme 2).

The catalyst, $VO(OTf)_2$, would be released by proton transfer to the vanadyl enolate, and the *O*-acetyl phosphonium center in **II** would be neutralized to the corresponding phosphonate by acetate, leading to the enol form of γ-oxo-phosphonate **III** along with generation of Ac_2O. The intermediate **III** would spontaneously tautomerize to its corresponding γ-oxo-phosphonate.[23]

The Friedel−Crafts alkylation reaction of electron-rich (hetero)arenes with α,β-unsaturated carbonyls (i.e., Friedel−Crafts-type conjugate addition) is a powerful C−C bond-forming methodology in organic synthesis.[24] In addition to the C−X bond construction from the catalytic hetero-Michael additions demonstrated above, we finally investigated the feasibility of conjugate additions of heteroarenes such as indoles, furans, and thiophenes to enones in view of their ample applications to access biologically active templates, particularly, indole alkaloids,[25] in nature. To our delight, all the targeted conjugate additions went to completion in 11−36 h at ambient temperature in 1.0 M CH_2Cl_2 with 10 mol % of $VO(OTf)_2$ (Table 3). In general, 3-substituted indoles such as 3-methylindole are less reactive than the corresponding unsubstituted ones (compare entries 1 and 2). In addition, thiophenes are less reactive than the corresponding furans (compare entries 3 and 4). Electron-rich benzenes as represented by 1,3,5-trimethoxybenzene are also amenable to the Friedel−Crafts-type conjugate addition. This compound adds to 2-cyclohexenone smoothly at ambient temperature in 41 h, leading to the C−C bond-forming adduct **3h′** in 96% yield (entry 5).

Table 3. Friedel−Crafts-Type Additions of (Hetero)aromatics to Enones Catalyzed by $VO(OTf)_2$[a]



entry	Michael acceptor	R^1R^2N-H	time, h	yield,[a] %
1	**1**		11	90 (**1e'**)
2	**3**		20	73 (**3g'**)
3	**4**		19	98 (**4b'**)
4	**5**		36	85 (**5b'**)
5	**3**		41	96 (**3h'**)

[a] Asterisk signifies the reaction site. [b] Isolated, purified yield.

In conclusion, we have documented the first successful report of using $VO(OTf)_2$ as a catalyst for the Michael additions. Very weak N-centered nucleophiles can be utilized for the new catalytic aza-Michael processes. Furthermore, hydrogen phosphines/phosphates become useful Michael donors when catalyzed by $VO(OTf)_2$. A new in situ generated acetylphosphite protocol catalyzed by $VO(OTf)_2$ allows one to utilize hydrogen phosphites for direct conjugate additions to enones.

Acknowledgment. We thank the National Science Council of Taiwan for a financial support of this research.

Supporting Information Available: Spectral data and characterization for products **1a′**−**e′**, **3a′**−**h′**, **4a′**,**b′**, and **5a′**,**b′**, **6a′**, and **7a′** are included. The material is available free of charge via the Internet at http://pubs.acs.org.

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(22) About 15−20% yields of the addition products **3c′** and **4a′** were isolated without the addition of vanadyl triflate at 70 °C for 48 h.

(23) Overall, 1 equiv of Ac_2O is needed in the acetylation of hydrogen phosphite and 1 equiv of HOAc (the byproduct in the acetylation step) is needed for the protonation of **II**.

(24) For reviews, see: (a) Olah, G. A.; Kishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 293−339. (b) Jørgensen, K. A. *Synthesis* **2003**, 1117.

(25) (a) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison Wesley Longman: Essex, 1997. (b) For Sc(III)-catalyzed enantioselective indole Friedel−Crafts alkylations, see: Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942.