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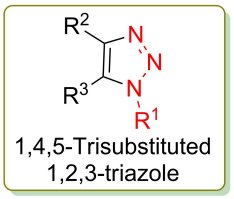
An Organocatalytic Vinyl Azide-Carbonyl [3 + 2]-Cycloaddition: High-yielding Synthesis of Fully Decorated *N*-Vinyl-1,2,3-Triazoles

Dhevalapally B. Ramachary,* G. Surendra Reddy, Swamy Peraka, and Jagjeet Gujral

Abstract: For the first time, an enolate-mediated organocatalytic vinyl azide–carbonyl [3+2]-cycloaddition (OrgVACC) of various ketones/aldehydes with vinyl azides is reported. It is an efficient intermolecular reaction with excellent outcomes with reference to rate, yield, selectivity, operation simplicity, substrates scope, simple catalyst and vast applications.

Recently, functionalized 1,2,3-triazoles have become important molecules with many unique chemical/physical properties and are widely used as pharmaceuticals due to their bio-similarity with amide bonds.[1] Fully decorated 1,2,3-triazoles have found vast applications in organic, bio-organic, polymer, medicinal, pharmaceutical and material chemistry.[2] Pharmacological outcome of 1,2,3-triazoles is completely based on their 1,4-, 1,5- or 1,4,5-substitutions and due to this reason, the design and development of more general green catalytic methods for their selective fully decorated synthesis are of significant interest (Scheme 1).[3-6]



1,4,5-Trisubstituted 1,2,3-triazole

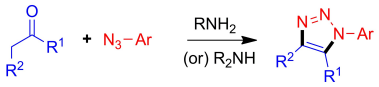
- HIV protease inhibitors
- Anticancer drugs
- Anti-tuberculosis drugs
- Antifungal agents
- Antibacterial drugs
- Histone deacetylase inhibitors
- Bioorthogonal probes

(1)

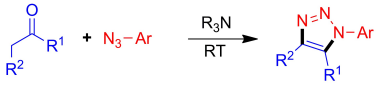
For example, 1,4- or 1,5-disubstituted 1,2,3-triazoles and 1,4,5-trisubstituted 1,2,3-triazoles have significant role in pharmaceutical chemistry [Eq. (1)] and as mentioned previously, their drug properties mainly depend on their aliphatic or aromatic substitutions.[2] Already four 1,2,3-triazole-based drugs [tazobactam, solithromycin, cefatrizine and rufinamide] are currently in use,[7] which is inspiring us to develop novel functionalized 1,2,3-triazoles for more properties through organocatalysis. Herein, we showed interest to develop a single-step general catalytic protocol for high-yielding regioselective synthesis of 1,4,5-trisubstituted *N*-vinyl-1,2,3-triazoles and 1,4-disubstituted *N*-vinyl-1,2,3-triazoles. Functionalized *N*-vinyl-1,2,3-triazoles are not only inspiring due to their novel functionality, but also can become suitable starting materials for *N*-alkyl-1,2,3-triazoles synthesis (eq. a-c, Scheme 1). Very little is known about the regioselective catalytic synthesis of functionalized *N*-vinyl-1,2,3-triazoles. In the previous synthetic methods, copper-catalyzed alkyne-vinylazide or alkyne-β-haloalkyl azide cycloaddition gave moderate to poor yields,[8] gold-catalyzed 1,2,3-triazole addition to alkynes gave good yields at higher temperature,[9] and pre-formed enamine/enolate cycloaddition with vinyl azide gave moderate to poor yields for longer reaction times.[10] These drawbacks stimulated us to develop a general catalytic protocol for high-yielding regioselective synthesis of 1,4,5-/1,4-substituted *N*-vinyl-1,2,3-triazoles.[5] Herein, we revealed an operationally simple, rapid, and general protocol "organocatalytic vinyl azide–carbonyl [3+2]-cycloaddition (OrgVACC)" for the selective synthesis of fully decorated *N*-vinyl-1,2,3-triazoles from the vinyl azides and simple deoxybenzoins, arylacetones or arylacetaldehydes utilizing organocatalyst (eq. d, Scheme 1).[5a]

Scheme 1: Reaction design for the vinyl azide-carbonyl [3+2]-cycloaddition.

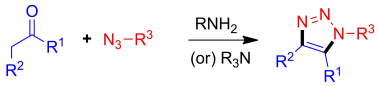
a) Enamine-mediated [3+2]-cycloaddition with aryl azides: Ramachary-Bressy-Wang



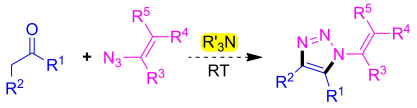
b) Enolate-mediated [3+2]-cycloaddition with aryl azides: Ramachary



c) Enamine/Enolate-mediated [3+2]-cycloaddition with alkyl azides: Not known



d) Enolate-mediated [3+2]-cycloaddition with vinyl azides: **This work**



We commenced the prior optimization of OrgVACC by screening the organocatalysts for the cycloaddition reaction of deoxybenzoin **1a** with 1.2 equiv. of α-azidostyrene **2a** (Table 1). [3+2]-Cycloaddition reaction of **1a** with **2a** in DMSO under 10-mol% of proline **3a**-catalysis at 25 °C for 17 h furnished the expected *N*-vinyl-1,2,3-triazole **4aa** as a single regioisomer in only 3% yield (Table 1, entry 1). The same reaction at 25 °C for 17 h under 10-mol% of diethyl amine **3b**, or pyrrolidine **3c**-catalysis furnished the *N*-vinyl-1,2,3-triazole **4aa** in 8%, and 45% yields, respectively (Table 1, entries 2-3). After obtaining poor

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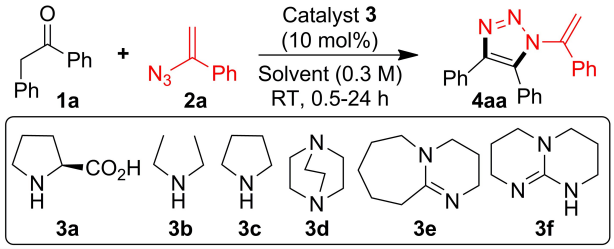
Supporting information (experimental procedures and analytical data for all new compounds) for this article is given via a link at the end of the document.

results with secondary amine catalysts **3a-c** through enamine-formation, based on our previous experience,[5] we thought of exploring the same reaction through in situ enolate formation, using some *tert*-amines **3d-f** and non-amine bases **3g-h** as the catalysts for the OrgVACC reaction (Table 1). Under DABCO **3d**-catalysis, cycloaddition reaction of **1a** with **2a** in DMSO at 25 °C for 17 h furnished the expected product **4aa** in only 10% yield (Table 1, entry 4). Intriguingly, the [3+2]-cycloaddition reaction of **1a** with **2a** in DMSO under 10-mol% of DBU **3e**-catalysis at 25 °C in just 0.5 h furnished the *N*-vinyl-1,2,3-triazole **4aa** in 93% yield (Table 1, entry 5). The same OrgVACC reaction under the catalysis of DBU **3e** in other solvents like DMF, $CHCl_3$ and CH_3CN at 25 °C for 17 h furnished **4aa** in 90%, 5% and 22% yields, respectively (Table 1, entries 6, 7 and 8). Same OrgVACC reaction under the catalysis of triazabicyclodecene **3f** in DMSO at 25 °C for 8 h furnished **4aa** in 89% yield (Table 1, entry 9). Interestingly, the reaction under 10-mol% of non-amine bases of K_2CO_3 **3g** and *t*BuOK **3h**-catalysis in DMSO furnished the *N*-vinyl-1,2,3-triazole **4aa** in good yields at 25 °C for 13 and 0.5 h, respectively (Table 1, entries 10-11). No cycloaddition reaction was observed under self- or autocatalytic conditions in DMSO even after 24 h at 25 °C (Table 1, entry 12). Finally, we envisioned the optimized condition to be 25 °C in DMSO under 10-mol% of DBU **3e**-catalysis, which furnished the single isomer of fully decorated *N*-vinyl-1,2,3-traizole **4aa** in 93% yield from **1a** and **2a** (Table 1, entry 5).

Table 1: Reaction optimization.[a]

[a] Reactions were carried out in solvent (0.3 M) with 1.2 equiv. of **2a** relative to

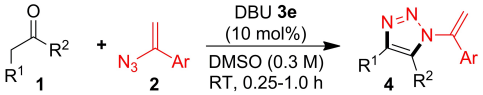


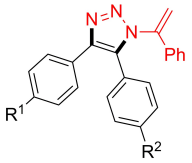
Entry	Catalyst **3**	Solvent	*t* [h]	Yield **4aa** [%][b]
1[c]	**3a**	DMSO	17	3
2[c]	**3b**	DMSO	17	8
3[c]	**3c**	DMSO	17	45
4[c]	**3d**	DMSO	17	10
5	**3e**	DMSO	0.5	93
6	**3e**	DMF	17	90
7[c]	**3e**	$CHCl_3$	17	5
8[c]	**3e**	CH_3CN	17	22
9	**3f**	DMSO	8.0	89
10	K_2CO_3 **3g**	DMSO	13	87
11	*t*BuOK **3h**	DMSO	0.5	88
12[c]	–	DMSO	24	–

the **1a** (0.3 mmol) in the presence of 10-mol% of catalyst **3**. [b] Yield refers to the column-purified product. [c] Ketone **1a** and azide **2a** was not consumed totally.

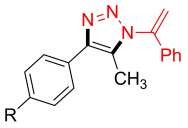
Table 2: Ketone and vinyl azide scope.[a]

[a] Reactions were carried out in DMSO (0.3 M) with 1.2 equiv. of **2** relative to



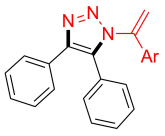


4ba: R^1 = Br, R^2 = Me (0.75 h; 92%)
4ca: R^1 = H, R^2 = Cl (0.5 h; 93%)
4da: R^1 = NO_2, R^2 = H (0.5 h; 90%)



4ea: R = H (0.5 h; 95%)
4fa: R = CH_3 (0.5 h; 90%)
4ga: R = OCH_3 (0.6 h; 90%)
4ha: R = Cl (0.6 h; 90%)
4ia: R = NO_2 (0.5 h; 92%)

4ja: R^1 = 2-naphthyl, R^2 = CH_3 (0.5 h; 90%)
4ka: R^1 = Ph, R^2 = $CH_2CH_2CH_3$ (0.5 h; 80%)



4ab: Ar = 4-FC_6H_4 (0.25 h; 85%)
4ac: Ar = 4-ClC_6H_4 (0.75 h; 80%)
4ad: Ar = 4-MeC_6H_4 (0.5 h; 85%)
4ae: Ar = 2-MeC_6H_4 (0.6 h; 82%)
4af: Ar = 4-$OMeC_6H_4$ (1.0 h; 55%)
4ag: Ar = 2-naphthyl (0.7 h; 86%)
4ah: Ar = 4-$PhC_6H_4OCH_2$ (0.75 h; 75%)
4ai: Ar = 4-$NO_2C_6H_4OCH_2$ (0.5 h; 80%)

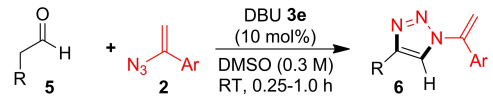
the **1** (0.3 mmol) in the presence of 10-mol% of **3e** and yield refers to the column-purified product.

With the best catalytic conditions in hand, the scope and generality of the enolate-mediated OrgVACC reaction were investigated. Firstly, substituted deoxybenzoins **1b-d** were reacted with α-azidostyrene **2a** catalyzed by 10-mol% of DBU **3e** at 25 °C in DMSO for 0.5-0.75 h (Table 2, entries 1-3). Intriguingly, the deoxybenzoins containing different functional groups (H, alkyl, halogen and NO_2) **1b-d** furnished the expected fully substituted *N*-vinyl-1,2,3-traizoles **4ba-da** in excellent yields within 0.5-0.75 h (Table 2, entries 1-3). Further, DBU **3e**-catalyzed OrgVACC reaction of substituted arylacetones **1e-i** with α-azidostyrene **2a** at 25 °C in DMSO for 0.5-0.6 h furnished the fully substituted *N*-vinyl-1,2,3-traizoles **4ea-ia** in very good yields (Table 2, entries 4-8). In this reaction, we did not observe any substitution effect on the phenyl ring and OrgVACC reaction worked well for different substitutions (H, CH_3, OCH_3, Cl and NO_2) of phenylacetones **1e-i** (Table 2, entries 4-8). In a similar manner, functionalized arylketones, 1-(naphthalen-2-yl)propan-2-one **1j** and 1-phenylpentan-2-one **1k** with **2a** furnished the functionally rich *N*-vinyl-1,2,3-traizoles **4ja** and **4ka** in very good yields within 0.5 h (Table 2, entries 9-10). After comprehending the OrgVACC reaction by probing the electronic factors of deoxybenzoins or arylacetones **1a-k** with **2a**, we further showed interest to investigate the electronic factors of α-azidostyrenes **2b-i** with deoxybenzoin **1a** (Table 2, entries 11-18). Functionalized α-azidostyrenes **2b-g** were reacted with deoxybenzoin **1a** catalyzed by 10-mol% of DBU **3e** at 25 °C in DMSO for 0.25-1.0 h (Table 2, entries 11-16). Uneventfully, the α-azidostyrenes containing different functional groups on the aryl ring (4-F, 4-Cl, 4-Me, 2-Me,

4-OMe, and 2-naphthyl) **2b-g** furnished the expected fully substituted *N*-vinyl-1,2,3-triazoles **4ab-ag** in excellent to good yields (Table 2, entries 11-16). Though the *N*-vinyl-1,2,3-triazoles **4ab-ag** were obtained in good yields for all the different substituted α-azidostyrenes **2**, reaction rate and yield were noticeably decreased with EDG substitution. Interestingly, the DBU **3e**-catalyzed OrgVACC reaction of **1a** with aliphatic vinyl azides 4-((2-azidoallyl)oxy)-1,1'-biphenyl **2h** and 1-((2-azidoallyl)oxy)-4-nitrobenzene **2i** furnished the expected *N*-vinyl-1,2,3-triazoles **4ah** in 75% and **4ai** in 80%, respectively under the optimized reaction conditions (Table 2, entries 17-18). This serves one of the important applications from OrgVACC, where we can generate a library of aliphatic substituted *N*-alkyl-1,2,3-triazoles from the corresponding *N*-vinyl-1,2,3-triazoles **4**. The structure and regiochemistry of the OrgVACC products **4** were established by NMR analysis and also finally confirmed by the X-ray structure analysis on **4ia** as shown in Figure S1 (see the Supporting Information).[11]

Table 3: Aldehyde and vinyl azide scope.[a]

[a] Reactions were carried out in DMSO (0.3 M) with 1.2 equiv. of **2** relative to the **5** (0.3 mmol) in the presence of 10-mol% of **3e** and yield refers to the column-purified product.



6aa: Ar = C_6H_5 (0.5 h; 90%)
6ba: Ar = 4-FC_6H_4 (0.25 h; 90%)
6ca: Ar = 4-BrC_6H_4 (0.75 h; 88%)
6da: Ar = 2-MeC_6H_4 (0.75 h; 85%)
6ea: Ar = 4-$OMeC_6H_4$ (0.75 h; 82%)
6fa: Ar = 2-$NO_2C_6H_4$ (0.5 h; 85%)
6ga: Ar = 2-naphthyl (0.75 h; 80%)

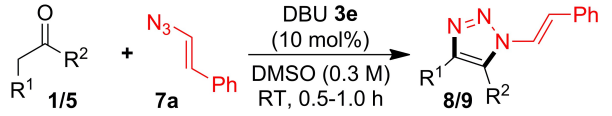
6ha: (6.0 h; 85%) @ KO^{t}Bu-catalysis

6ab: Ar = 4-FC_6H_4 (0.25 h; 85%)
6ac: Ar = 4-ClC_6H_4 (0.75 h; 80%)
6ad: Ar = 4-MeC_6H_4 (0.5 h; 87%)
6ae: Ar = 2-MeC_6H_4 (0.5 h; 85%)
6af: Ar = 4-$OMeC_6H_4$ (1.0 h; 50%)
6ag: Ar = 2-naphthyl (0.5 h; 88%)

After investigation of the OrgVACC reaction by probing the electronic factors of alkyl or aryl ketones **1** with α-azidostyrenes **2**, we further showed interest to investigate the electronic factors of aryl or alkyl acetaldehydes **5a-h** by reacting with α-azidostyrenes **2** in the OrgVACC reaction (Table 3). Fascinatingly, the reaction of aryl acetaldehydes **5a-g,** containing different functional groups of alkyl, halogen, EWG's, and EDG's on aryl ring with simple α-azidostyrene **2a** under 10-mol% of **3e**-catalysis furnished the single isomer of 1,4-disubstituted-*N*-vinyl-1,2,3-triazoles **6aa-ga** in excellent yields similar to the deoxybenzoin **1a**/phenylacetone **1e** (Table 3, entries 1-7). Although, the aliphatic aldehyde, 3-phenylpropanal **5h** didn't furnished the expected product under **3e**-catalysis, under the catalysis of *t*BuOK **3h** at 25 °C for 6.0 h furnished the expected *N*-vinyl-1,2,3-triazole **6ha** in 85% yield (Table 3, entry 8). After these results, we further investigated the scope of this reaction by treating phenylacetaldehyde **5a** with functionalized α-azidostyrenes containing different functional groups on the aryl ring (4-F, 4-Cl, 4-Me, 2-Me, 4-OMe, and 2-naphthyl) **2b-g** to furnish the 1,4-disubstituted-*N*-vinyl-1,2,3-triazoles **6ab-ag** in excellent to good yields (Table 3, entries 9-14). The Table 3 results demonstrate the broad scope of this protocol covering a structurally diverse group of aryl acetaldehydes **5** and α-azidostyrenes **2** to furnish the 1,4-disubstituted-*N*-vinyl-1,2,3-triazoles **6**. In most of the cases, the product **6** yields obtained were excellent compared to the previously available multi-step methods.[8-10] The structure and regiochemistry of the products **6** were established by NMR analysis and also finally confirmed by the X-ray structure analysis on **6ag** (Figure S2, see the Supporting Information).[11]

Table 4: β-Azidostyrene scope.[a]

[a] Reactions were carried out in DMSO (0.3 M) with 1.2 equiv. of **7a** relative to the **1/5** (0.3 mmol) in the presence of 10-mol% of **3e** and yield refers to the column-purified product.



8aa: R^1 = H, R^2 = H (0.65 h; 85%)
8ba: R^1 = Br, R^2 = Me (1.0 h; 92%)
8ca: R^1 = H, R^2 = Cl (0.82 h; 95%)

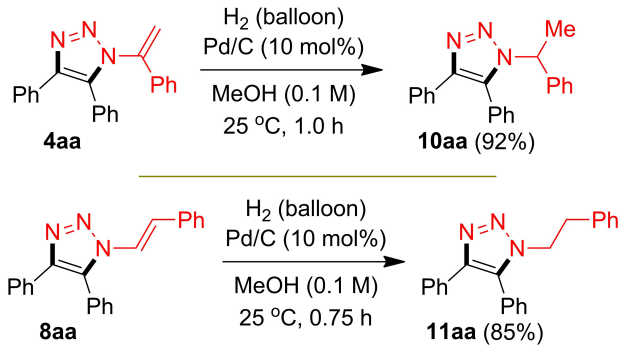
8ea: R = H (0.75 h; 85%)
8fa: R = CH_3 (0.65 h; 90%)
8ga: R = OCH_3 (0.65 h; 85%)
8ha: R = Cl (0.75 h; 92%)
8ia: R = NO_2 (0.5 h; 70%)

8ja: R^1 = 2-naphthyl, R^2 = CH_3 (0.65 h; 90%)
8ka: R^1 = Ph, R^2 = $CH_2CH_2CH_3$ (0.5 h; 90%)

9aa: (0.5 h; 90%)

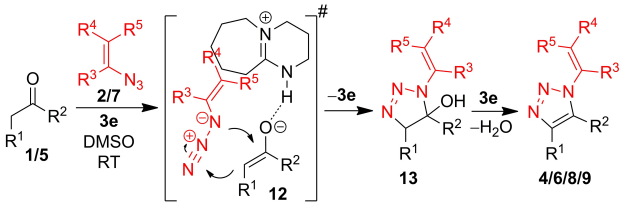
To further develop the diverse library of fully decorated *N*-vinyl-1,2,3-triazoles **8/9** and also to understand the electronic factors of β-azidostyrenes **7** in the OrgVACC reaction, we have chosen β-azidostyrene **7a**, which is more reactive towards carbonyls compared to α-azidostyrenes **2** due to the linear conjugation (Table 4). The OrgVACC reaction of deoxybenzoin **1a** with β-azidostyrene **7a** under the optimized conditions furnished the expected *N*-vinyl-1,2,3-triazole **8aa** in 85% yield (Table 4, entry 1). We have also tested two more examples of halogen-, and methyl-substituted deoxybenzoins **1b-c** for the OrgVACC reaction with **7a**, which furnished the *N*-vinyl-1,2,3-triazoles **8ba-ca** in excellent yields (Table 4, entries 2-3). The OrgVACC reaction of hydrogen-, methyl-, methoxy-, chloro-, and nitro-substituted arylketones **1e-i** with **7a** under the **3e**-catalysis furnished the fully decorated *N*-vinyl-1,2,3-triazoles **8ea-ia** in 70-92% yields without showing much of electronic factors (Table 4, entries 4-8). Likewise, functionalized arylketones, 1-(naphthalen-2-yl)propan-2-one **1j** and 1-phenylpentan-2-one **1k** with **7a**

furnished the 1,4,5-trisubstituted-*N*-vinyl-1,2,3-traizoles **8ja** and **8ka** in 90% yield, respectively (Table 4, entries 9-10). Reaction of phenylacetaldehyde **5a** with β-azidostyrene **7a** under 10-mol% of **3e**-catalysis furnished the single isomer of 1,4-disubstituted-*N*-vinyl-1,2,3-triazole **9aa** in 90% yield (Table 4, entry 11).



Scheme 2: Reaction application.

The importance of OrgVACC reactions was further exemplified by synthesizing compounds **10aa** and **11aa** (Scheme 2).[2] Catalytic hydrogenation of 1,4,5-trisubstituted-*N*-vinyl-1,2,3-triazole **4aa** with hydrogen balloon under 10-mol% of Pd/C in methanol at 25 °C for 1.0 h furnished the functionalized *N*-alkyl-1,2,3-triazole **10aa** in 92% yield. Similarly, treatment of **8aa** with hydrogen balloon in the presence of Pd/C in methanol at 25 °C for 1.0 h furnished the functionalized *N*-alkyl-1,2,3-triazole **11aa** in 85% yield. On the contrary, the literature synthesis of this triazole **11aa** starting from the diphenylacetylene and (2-azidoethyl)benzene requires costly Ru-catalyst, high temperature and a long reaction time (Scheme 2).[12] These results clearly demonstrate the exceptional advantages and more applications of OrgVACC protocol, which enables the simple high-yielding synthesis of fully substituted *N*-alkyl-1,2,3-triazoles, which are not easily accessible from other methods.



Scheme 3: Reaction mechanism.

The mechanism for the OrgVACC is illustrated in Scheme 3. Reaction of the deoxybenzoins/arylacetones/arylacetaldehydes **1/5** with catalyst DBU **3e** in DMSO generates the stable enolate **12**, which on in situ treatment with vinyl-azides **2/7** furnishes selectively the functionally-rich adduct 1,2,3-triazolines **13** by [3+2]-cycloaddition.[13] The adduct **13** further transforms into the fully decorated *N*-vinyl-1,2,3-triazoles **4/6/8/9** through rapid elimination of water under ambient conditions.

In summary, we have developed a versatile organocatalytic enolate-mediated vinyl azide-carbonyl [3+2]-cycloaddition to furnish the functionally-rich 1,4,5-trisubstituted-*N*-vinyl-1,2,3-triazoles and 1,4-disubstituted-*N*-vinyl-1,2,3-triazoles with medicinally useful functional groups. Present method of OrgVACC highlights the metal-free conditions, high rate and selectivity, and easy access to the library of *N*-vinyl-1,2,3-triazoles. Moreover, many of the reported syntheses have the disadvantage of requiring multiple synthetic steps, harsh reaction conditions, heavy metals and less available unsymmetric internal alkynes; therefore, this OrgVACC protocol is very convenient to practice. Further work is in progress to utilize the enolate-mediated OrgVACC reactions in medicinal and material chemistry.

Experimental Section

Experimental procedures, and compound characterization data (^{1}H NMR, ^{13}C NMR, and HRMS). This material is available free of charge in the Supporting Information.

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Entry for the Table of Contents

N-Vinyl-1,2,3-Triazoles

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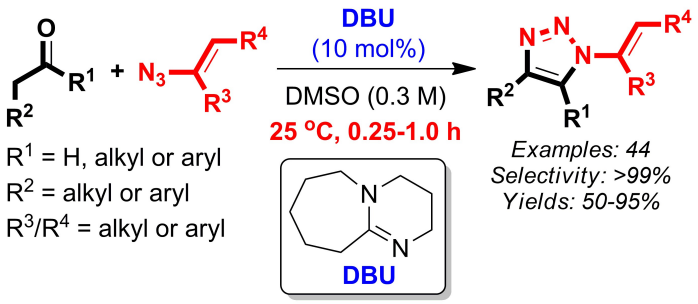
An Organocatalytic Vinyl Azide-Carbonyl [3+2]-Cycloaddition: High-yielding Synthesis of Fully Decorated *N*-Vinyl-1,2,3-Triazoles



An enolate-mediated organocatalytic vinyl azide–carbonyl [3+2]-cycloaddition (OrgVACC) of various ketones/aldehydes with vinyl azides is reported. It is an efficient catalytic intermolecular OrgVACC reaction for the synthesis of *N*-vinyl-1,2,3-triazoles.