Propargyl α-aryl-α-diazoacetates as robust reagents for the effective C-H bond functionalization of 1,3-diketones via scandium catalysis

Balu S. Navale, Debasish Laha, Ramakrishna G. Bhat

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Graphical Abstract

Propargyl *α*-aryl-*α*-diazoacetates as robust reagents for the effective C-H bond functionalization of 1,3-diketones via scandium catalysis

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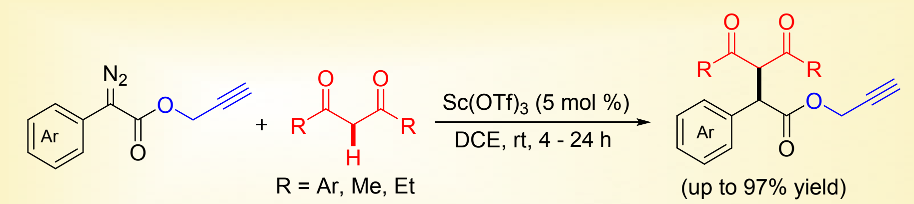

- Propargyl *α*-aryl-*α*-diazoacetates-Robust reagents
- Works with deactivated substrates
- Less prone for side reactions
- Low Catalyst loading (5 mol %)
- Total of 27 examples and gram scale synthesis

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Propargyl α-aryl-α-diazoacetates as robust reagents for the effective C-H bond functionalization of 1,3-diketones via scandium catalysis

Balu S. Navale, Debasish Laha and Ramakrishna G. Bhat*

Department of Chemistry, Main Building, Indian Institute of Science Education and Research (IISER)-Pune, Dr. Homi Bhabha Road, Pashan, Pune, 411008, Maharashtra, India

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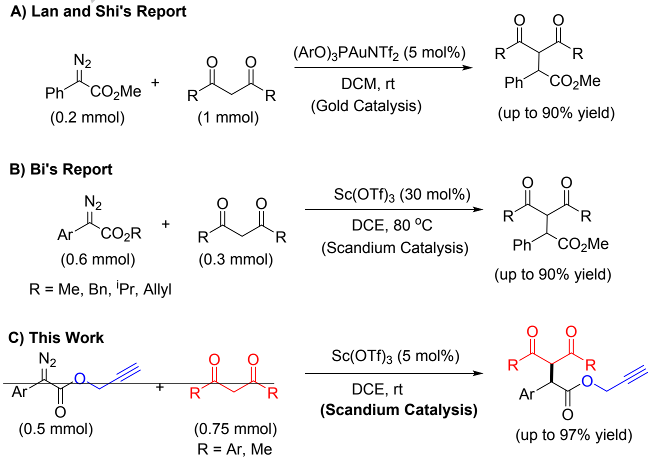
ABSTRACT

Propargyl α-aryl-α-diazoacetate a new class of reagent is developed for the effective C-H bond functionalization of 1,3-diketones at room temperature. The combination of scandium triflate and propargyl α-aryl-α-diazoacetate proved to be efficient catalyst-reagent system for the controlled C-H bond functionalization to afford 1,3-dicarbonyl alkylation. The protocol uses inexpensive Sc(OTf)$_3$ (5 mol%) and the reaction did not require the use of expensive catalysts or ligands and worked efficiently at room temperature. The practicality of the protocol has been demonstrated by the gram scale synthesis.

1. Introduction

Selective C-H bond functionalization for the construction of new C-C bonds presents an alternative and powerful strategy to the traditional methods in organic synthesis. The direct C-H bond functionalization has several advantages and has attracted a great attention from the synthetic community.[1,2] The direct C-H bond functionalization reduces the number of synthetic steps and the pre-activation of starting materials could be avoided to increase the overall atom-efficiency. It has rapidly become one of the powerful tools for the synthesis and modification of complex molecules.[3] A great progress has been made in this field using different transition metal catalysts.[4] However, identifying and developing a suitable combination of catalyst and reagent system for the selective C-H bond functionalization is always a challenging task. The diazo compounds have been established as versatile reagents for various metal-catalyzed reactions.[5] Davies is one of the pioneers who embarked on comprehensive investigations of the scope of intermolecular C-H bond functionalization using diazo compounds.[6] The C-H bond functionalization using α-diazo esters normally proceeds via transient metal-carbenoid species, which are usually formed by the reaction with transition-metal complexes.[7] The transition metals such as rhodium,[8] copper,[9] silver[10] and recently gold[11] have been successfully explored for the decomposition of α-diazo esters to achieve the C-H bond functionalization. Different carbon nucleophiles have been explored for the intermolecular C-H bond functionalization with donor/acceptor type α-diazo esters.[11g,12]

Reactive 1,3-dicarbonyl compounds are very useful scaffolds and they have been utilized for the transition-metal catalyzed oxidative C-H bond functionalization to access useful compounds.[13] However, these useful protocols need oxidants, excess substrates and high temperature for the effective transformation. In the year 2014, Lan and Shi, and co-workers elegantly presented the first gold-catalyzed C-H functionalization of 1,3-dicarbonyl compounds with α-aryl-α-diazoacetate (see Fig 1A).[14]



- Propargyl α–aryl-α–diazoacetate-Robust reagent
- C-H functionalization at room temperature
- Works with deactivated substrates
- Less prone for Side reactions
- Low Catalyst loading (5 mol%)

Fig.1 C-H bond functionalization of 1, 3-dicarbonyl compounds with α-aryl-α-diazoacetates-Influence of ester groups

It was demonstrated that the reaction followed the gold catalyzed decomposition of α-aryl-α-diazoacetate via the

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* Dr. Ramakrishna G. Bhat; Tel.: +91-20-25908092; fax: + 91-20-25898022; e-mail: rgb@iiserpune.ac.in

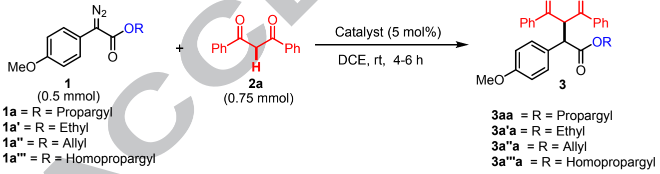
formation of a carbophilic carbocation. However, there is a great challenge to develop novel catalyst and reagent systems that are easily available and less expensive. A lot more efforts is needed to avoid the use of any expensive catalysts and ligands to make the protocol simple and practical which work at room temperature under mild conditions. Although, coinage metals and few of the heavy transitional-metals have been successfully explored for the C-H bond functionalization of *α*-diazo esters, alternative yet useful catalyst systems are desirable. Group 3 transition metals, e.g., scandium and lanthanides, have been used as environmentally friendly Lewis acid catalysts or promoters for a variety of chemical transformations.[15]

Scandium catalysis has been promising and scandium triflate has been explored for the reactions of diazo compounds to achieve the successful C-H bond functionalization.[16] It would be very interesting to study the efficiency of scandium catalyst on the C-H bond functionalization of 1,3-dicarbonyl compounds with *α*-aryl-*α*-diazo esters. The main challenges of this type of reaction are to avoid the side reactions such as dimerization of *α*-diazo esters, formation of *α*-oxoesters and to minimize the catalytic amount of the metal catalyst. It would also be a challenging task to have a catalyst control over insertion processes such as C-H insertion over O-H insertion. While this manuscript was under preparation, Bi and Co-workers disclosed the C-H bond functionalization of 1,3-dicarbonyl compounds with *α*-aryl-*α*-diazoacetates via scandium catalysis using higher catalyst loading and excess of *α*-aryl-*α*-diazoacetates at elevated temperature (see Fig. 1B).[10e] Our group has been independently pursuing the development of catalyst-reagent system to expand the scope of C-H bond functionalization of *α*-diazo esters using early transition elements and lanthanides.[17] Despite many advances, still there are numerous limitations such as high reaction temperature, high substrate-reagent ratio, use of excess catalytic amount and expensive catalysts etc. Some of these limitations need to be overcome to make the protocols more practical and affordable. Herein, we report the discovery of propargyl *α*-aryl-*α*-diazoacetates as robust and useful new class of reagents for the C-H bond functionalization.

Results and discussion

At the outset, we began our investigation by choosing ethyl α-(4-methoxyphenyl)-α-diazoacetate **1a’** and 1,3-diketone **2a** (1,3-diphenyl-1,3-propanedione) as model substrates. The reaction of ethyl α-(4-methoxyphenyl)-α-diazoacetate **1a’** and 1,3-diketone **2a** in presence of $Cu(OTf)_2$ (5 mol%) in DCE at room temperature afforded the corresponding desired C-H functionalized product **3a’a** in 52% yield in 6 h (Entry 1, Table 1). While, the reaction in presence of gold catalyst [$(ArO)_3PAuNTf_2$ (5 mol%)] afforded the **3a’a** in moderate yield (36%, Entry 2, Table 1). Interestingly, $Sc(OTf)_3$ (5 mol%) catalyzed the reaction of ethyl α-(4-methoxyphenyl)-α-diazoacetate **1a’** (0.5 mmol) and 1,3-diketone 2a (0.75 mmol) to afford the desired product **3a’a** in 51% yield in 6 h at room temperature (See Entry 3, Table 1). A slight excess of unreacted **2a** was recovered during the purification. It was very encouraging that desired reaction worked at room temperature under scandium catalysis. Likewise, allyl α-(4-methoxyphenyl)-α-diazoacetate **1a’’** (0.5 mmol) and 1,3-diketone **2a** (0.75 mmol) reacted in presence of $Sc(OTf)_3$ (5 mol%) to afford the desired product **3a’’a** in 53% yield in 6 h at room temperature (See, Entry 4, Table 1). The reactions in presence of gold catalyst [$(ArO)_3PAuNTf_2$ (5 mol%)] afforded the desired products in modest yields (see Entries, 5, 6 Table 1). It is known in the literature that propargyl moiety is a weakly electron withdrawing group[18] and in this regard we planned to explore the effect of propargyl group in C-H bond functionalization of 1,3-dicarbonyl compounds. Propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1a** upon treatment with **2a** in presence of $Sc(OTf)_3$ (5 mol%) in DCE at room temperature afforded the corresponding **3aa** in relatively shorter reaction time with an excellent yield (96%, Entry 7, Table 1). Later, we screened various catalysts to explore the reactivity of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1a** (see Entries 8-14). $Cu(OTf)_2$ catalyzed the desired reaction affording **3aa** in 71% yield in 6 h, where as other catalysts found to be not useful. In order to confirm the catalytic efficiency of $Sc(OTf)_3$, and to rule out the possibility of the formation of trace amount of triflic acid in situ by the hydrolysis of $Sc(OTf)_3$ if any due to the moisture and its subsequent catalysis, we carried out the reaction of **1a** and **2a** in presence of catalytic amount triflic acid (Entry 15, Table 1).

Table 1 Optimization of the reaction conditions for C-H functionalization[a-d]

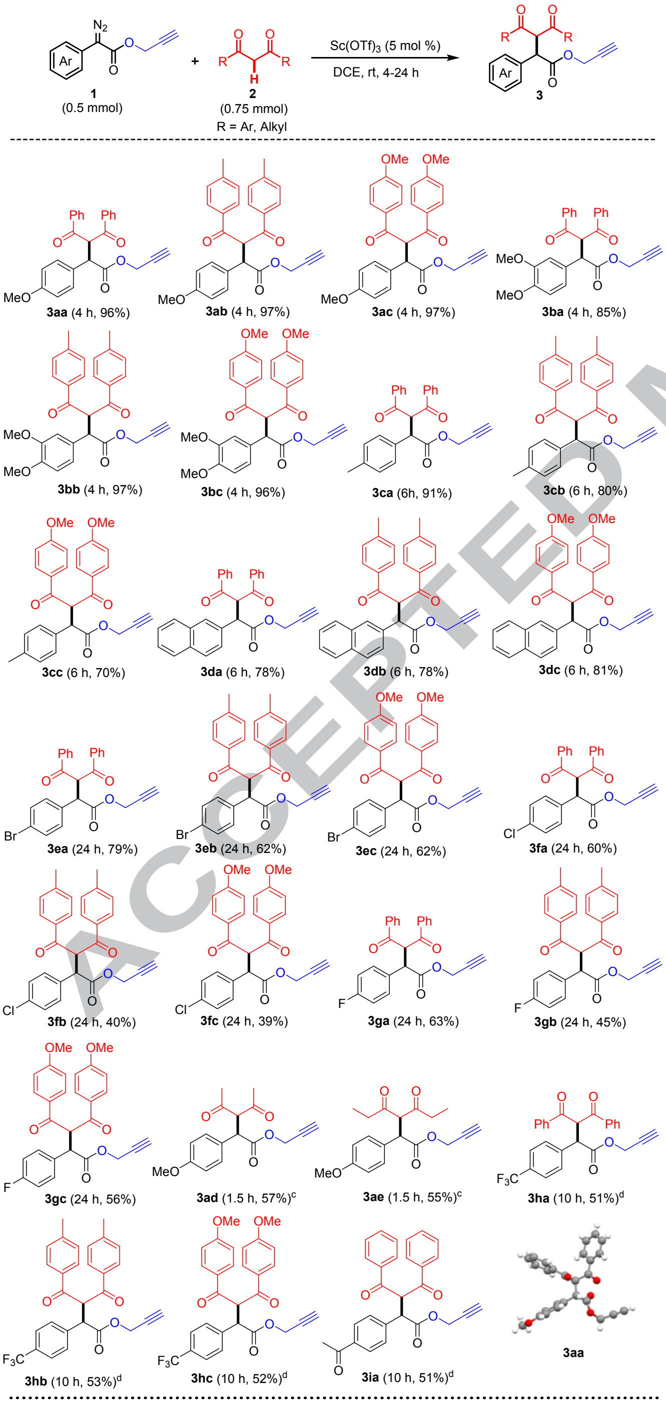


Entry	Catalyst	Substrate (1) R	Time (h)	Yield[b] (%)
1	$Cu(OTf)_2$	Ethyl	6	52
2	$(ArO)_3PAuNTf_2$	Ethyl	4	36
3	$Sc(OTf)_3$	Ethyl	6	51
4	$Sc(OTf)_3$	Allyl	6	53
5	$(ArO)_3PAuNTf_2$	Allyl	6	39
6	$(ArO)_3PAuNTf_2$	Propargyl	4	37
7	**$Sc(OTf)_3$**	**Propargyl**	**4**	**96**
8	$Bi(OTf)_3$	Propargyl	6	trace
9	$Cu(OTf)_2$	Propargyl	6	71
10	Dichloro(*p*-cymene)ruthenium(II) dimer	Propargyl	6	DC[c]
11	$Y(OTf)_3$	Propargyl	6	18
12	$In(OTf)_3$	Propargyl	6	68
13	$Rh_2(OAc)_4$	Propargyl	4	DC [c]
14	$Yb(OTf)_3$	Propargyl	6	Trace
15	Triflic acid	Propargyl	6	DC[c]
16	$Sc(OTf)_3$	Homopropargyl	6	73
17	No Catalyst	Propargyl	6	NR[d]

[a] Reaction conditions: *α*-Aryl-*α*-diazoacetate **1** (1 equiv., 0.5 mmol), 1,3-diketone **2a** (1.5 equiv., 0.75 mmol), DCE (3 mL) at room temperature, [b] Isolated yield after purification by column chromatography. [c] DC-Decomposed, [d] NR-no reaction.

Interestingly, the reaction led to the decomposition of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1a** in presence of triflic acid. The reaction of homopropargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1a'''** (0.5 mmol) and 1,3-diketone **2a** (0.75 mmol) in presence of $Sc(OTf)_3$ (5 mol%) afforded the corresponding product **3a'''a** in 73% yield in 6 h at room temperature (See, Entry 16, Table 1). The reaction did not work in absence of any catalyst (Entry 17, Table 1).

Table 2. Scope of propargyl *α*-aryl-*α*-diazoacetates for the effective C-H bond functionalization of 1,3-diketones[a-d]



[a]Reaction conditions: *α*-aryl-*α*-diazoacetate **1** (1 equiv., 0.5 mmol), 1,3-diketone **2** (1.5 equiv., 0.75 mmol), Sc(OTf)$_3$ (5 mol%) in DCE (3 mL) at room temperature under inert atmosphere, [b]Isolated yield after purification by column chromatography (Time and Yield are given in parenthesis), [c]reaction was carried out at 50 °C, [d]Sc(OTf)$_3$ (10 mol%) in DCE at 70 °C under inert atmosphere

Later, in order to optimize the reaction condition further, we carried out the reaction of **1a** and **2a** in presence of Sc(OTf)$_3$ in different solvents and among all the solvents, DCE proved to be the optimal solvent (See Appendix 1, ESI). The combination of propargyl *α*-aryl-*α*-diazoacetate **1** and scandium triflate as reagent-catalyst system proved to be efficient for the effective C-H bond functionalization of 1,3-diketones.

We observed that propargyl *α*-aryl-*α*-diazoesters and scandium catalyst worked synergistically to bring about desired C-H bond functionalization very efficiently at room temperature. Based on the exhaustive screening, propargyl *α*-aryl-*α*-diazoacetate **1** (0.5 mmol), 1,3-diketone **2** (0.75 mmol), Sc(OTf)$_3$ (5 mol%) in DCE at room temperature proved to be the optimum reaction condition. Encouraged by the initial success, we planned to explore the reactivity and scope of different propargyl *α*-aryl-*α*-diazoacetates for the effective C-H bond functionalization of 1,3-diketones. In order to study the protocol in more detail we synthesized various propargyl *α*-aryl-*α*-diazoacetates (**1a-1g**). Relatively, electron rich propargyl *α*-aryl-*α*-diazoacetates (**1a-1d**) reacted smoothly with different 1,3-diketones under the optimum reaction conditions to afford the corresponding desired products (**3aa-3dc**) in good to excellent yields (Table 2). Mildly electron deactivated substrates such as bromo-, chloro-, fluoro-propargyl *α*-aryl-*α*-diazoacetates (**1e-1g**) reacted smoothly with nucleophilic acyclic 1,3-diketones (**2a-2c**) successfully to afford the corresponding tricarbonyl compounds (**3ea-3ec, 3fa-3fc, 3ga-3gc**) in moderate to good yields (Table 2). It is very important to note that mildly electron deactivated substrates such as chloro-, fluoro-propargyl *α*-aryl-*α*-diazoacetates reacted under the reaction conditions at room temperature. Further, the treatment of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1a** with aliphatic 1,3-diketones (**2d, 2e)** afforded the corresponding desired products (**3ad, 3ae)** at slightly elevated temperature in moderate yields (Table 2). While, the reactions of few propargyl *α*-aryl *α*-diazoacetates (**1h, 1i**) containing electron withdrawing groups (CF$_3$, Ac) with different 1,3-diketones in presence of Sc(OTf)$_3$ (10 mol %) afforded the corresponding desired products (**3ha-3hc, 3ia**) in moderate yields at elevated temperature (70 °C). Surprisingly, the reactions of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1a** with cyclic 1,3-diketones (1,3-cyclohexanedione and 1,3-cyclopentanedione) under the optimum reaction conditions exclusively furnished the corresponding O-H insertion products. Based on the earlier findings,[10e] it is believed that the formation of *cis* enol is crucial for the formation of bidentate complex with the metal for facilitating the C-H insertion reaction of acyclic 1,3-diketones. While the cyclic ketone such as 1,3-cyclohexanedione may not be able to form effective bidentate complex as it is known to form *trans* enol[19] thus leading to O-H insertion product.

We observed that relatively electron rich propargyl *α*-aryl-*α*-diazoacetates (**1a-1d**) showed better reactivity in terms of yields under standard conditions. Both electron-rich and electron -deactivated/withdrawing propargyl *α*-aryl-*α*-diazoacetates tolerated the reaction conditions. We did not observe any side products such as carbene dimerization, *α*-oxoesters and azines during the C-H bond functionalization of 1,3-diketones under the optimal reaction conditions.

In order to extend the scope the methodology we carried out the reaction of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1a** and 1,3-diketone **2a** on a gram scale under optimum reaction conditions.The protocol proved to be scalable and worked smoothly to afford the corresponding desired product **3aa** in 87% yield (Scheme 1).

Scheme 1. Gram scale synthesis

Further, the structure of the compound **3aa** was unambiguously confirmed by single crystal X-ray analysis.[20] Based on the earlier literature report,[10e] we proposed the plausible reaction pathway.[21] The 1,3-diketone **2** interacts with the Sc(OTf)$_3$ to form the scandium enolate **I** and triflic acid as by-product. This eventually acts as a proton source to protonate the propargyl *α*-aryl-*α*-diazoacetate **1** to generate the intermediate diazonium ion **II**, which undergoes a facile nucleophilic attack by the scandium enolate **I** to afford the complex **III** (Scheme 2).

Scheme 2. Plausible reaction pathway for the scandium catalyzed C-H insertion

Eventually the reaction of triflate anion with complex **III** furnishes the desired product **3** by regenerating the catalyst (Scheme 2). We presume that unlike electron donating power of ethyl/methyl group in ester, relatively weak electron deactivating propargyl moiety played a significant role in enhancing the electrophilicity of the diazonium ion which eventually leads to the reactive carbocation towards the facile C-H insertion at room temperature.

Conclusions

In conclusion, we have developed the new reagent-catalyst controlled effective C-H bond functionalization to afford 1,3-dicarbonyl alkylation via scandium catalysis. We have developed a new series of *α*-aryl-*α*-diazoacetates with propargyl ester as the robust acceptor group and employed them as reagents for the effective C-H functionalization at room temperature. The protocol avoids the use of excess, expensive catalysts and ligands under practical conditions at room temperature. Practicality of the protocol has been demonstrated by the gram scale synthesis.

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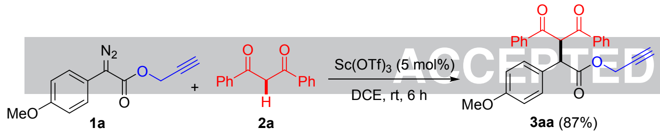

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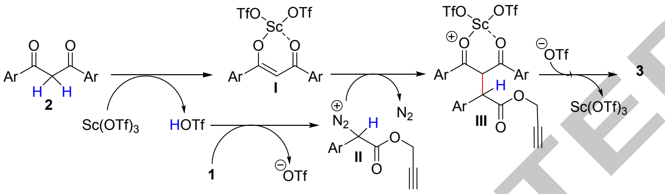

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[17] *We have been pursuing scandium triflate catalyzed C-H bond functionalizations under the sanctioned research project-Site-selective direct C-H bond functionalization by early transition metal-carbenoid insertion and its applications-EMR/2015/000909, SERB-DST Govt. of India.*

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[19] (a) A. Yigev, Y. Mazur, J. Org. Chem. 32 (1967) 2162; (b) M. Curini, F. Epifano, S. Genovese, Tetrahdron Lett. 47 (2006) 4697

[20] *CCDC number of **3aa** is 1848209 The number contains all crystallographic details of this publication and is available free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html.*

[21] It is believed that the formation of *cis* enol is crucial for the formation of bidentate complex with the metal for facilitating the C-H insertion reaction of acyclic 1,3-diketones (See ref 10e).

Supplementary Material

Electronic Supplementary Information (ESI) available: [Experimental details, copies of ^{1}H and ^{13}C NMR spectrum of products]. See DOI:

Graphical Abstract

Highlights

- Efficient C-H bond functionalization of 1,3-diketones

Propargyl *α*-aryl-*α*-diazoacetates as robust reagents for the effective C-H bond functionalization of 1,3-diketones via scandium catalysis

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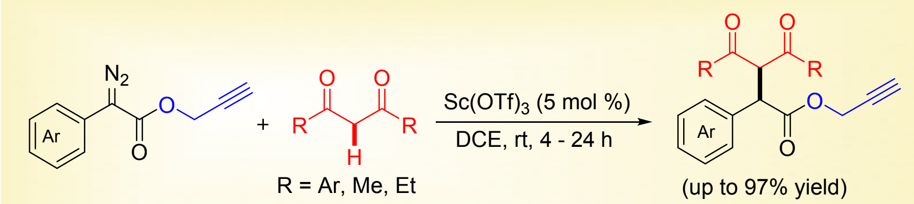
Balu S. Navale, Debasish Laha and Ramakrishna G. Bhat*



- Propargyl *α*-aryl-*α*-diazoacetates-Robust reagents
- Works with deactivated substrates
- Less prone for side reactions
- Low Catalyst loading (5 mol %)
- Total of 27 examples and gram scale synthesis

- Propargyl α-aryl-α-diazoacetate as a robust and novel reagent
- Catalytic amount (5 mol%) of $Sc(OTf)_3$ for the effective transformation
- Practical and scalable on gram scale
- Total of 27 examples with very good yields (up to 97%).