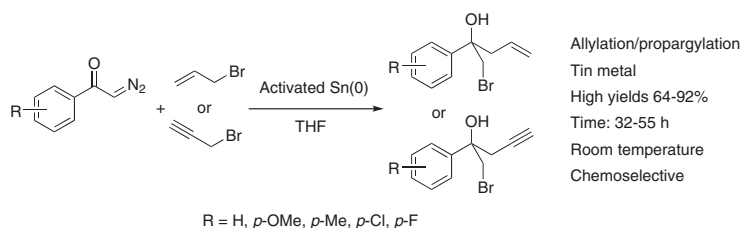


# Conversion of $\alpha$ -Diazoketones into 1-Bromo-2-alkyl- or 2-arylpent-4-en-2-ols using Tin-Mediated Allylation/Propargylation

Swapan Kumar Biswas<sup>\*a</sup>  
Sipak Joyasawal<sup>\*b</sup>

<sup>a</sup> Sree Chaitanya College, Habra, 743268, West Bengal, India  
skbiict@gmail.com

<sup>b</sup> Department of Chemistry, The University of Texas at San Antonio,  
San Antonio, Texas 78249, USA  
sipakjoyasawal@yahoo.com



Received: 02.03.2023

Accepted after revision: 04.04.2023

Published online: 03.04.2023 (Accepted Manuscript),  
08.05.2023 (Version of Record)

DOI: 10.1055/a-2068-5625; Art ID: SO-2023-03-0022-L



License terms:

© 2023. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution and reproduction, so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

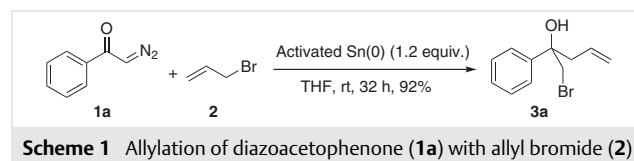
**Abstract** High-yielding and mild conditions are used to prepare of 1-bromo-2-alkyl- or 2-arylpent-4-en-2-ols/1-bromo-2-alkyl- or 2-arylpent-4-en-2-ols from  $\alpha$ -diazoketones. The reaction involves allylation/propargylation with successive bromide insertion using *in situ* generated allyltin bromide/or propargyltin bromide from activated tin metal and allyl/or propargyl bromide.

**Key words** tin metal, allylation, propargylation,  $\alpha$ -diazoketones, 1-bromo-2-alkyl-ol, 2-arylpent-4-en-2-ol

The use of  $\alpha$ -diazocarbonyl compounds in biologically active natural product synthesis and drug discovery is well known.<sup>1</sup> Extensive use of  $\alpha$ -diazocarbonyl compounds along with their wide commercial availability and their ease of conversion into active intermediates by extrusion of nitrogen under mild reaction conditions such as transition-metal catalysis, base, acid as well as photochemical and thermal conditions, has attracted organic chemists to use them as intermediates for the synthesis of complex organic molecules.<sup>2</sup> Utilization of metals in organic synthesis has led to the discovery of new reactions for making new carbon-carbon bonds; well known examples are magnesium metal in Grignard reactions and zinc in Negishi cross-coupling reaction. Therefore, a goal of chemists has always been to use tin, which is easily available as a nontoxic metal, to discover new organic reactions under mild reaction conditions.

Unique properties of tin and its low cost compared to most metals, created the potential for tin metal to become a champion among the metals with similar properties. The low toxicity of tin metal and favorable redox properties in the presence of air or oxygen at room temperature allowed its safe use in the laboratory. Moreover, a favorable heterophilicity of organotin reagents in organic reactions allows its use in organic reactions for substrates containing a wide range of versatile functional groups having nitrogen and oxygen.<sup>3</sup> Chemoselectivity using organotin reagents are high due to its low nucleophilicity.<sup>4</sup> Recent literature surveys showed that there are no reports for allylation or propargylation using *in situ* generated allyltin or propargyltin bromide and  $\alpha$ -diazoketones.<sup>5-7</sup> Our focus of research is to demonstrate that tin metal can be used effectively as organotin reagents for allylation/propargylation of  $\alpha$ -diazoketones.

When allylation of diazoacetophenone (**1a**) was attempted in the presence of tin metal in THF at room temperature using allyl bromide (**2**) the smooth formation of 1-bromo-2-phenylpent-4-en-2-ol (**3a**) was observed with high yield (92%, Scheme 1). In this manuscript, we describe the allylation and propargylation of  $\alpha$ -diazoketones with different functional groups using tin metal.

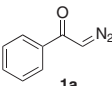

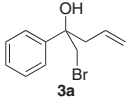
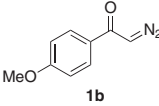

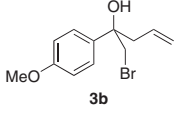
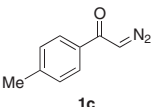

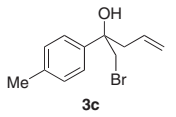
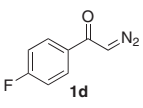

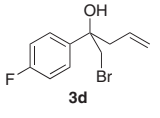
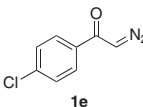

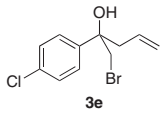
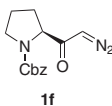

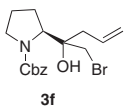
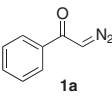

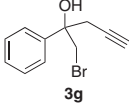
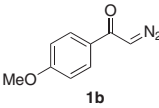

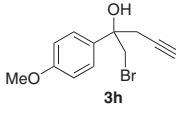
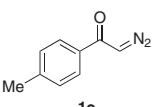

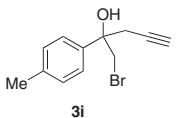


To evaluate the substrate scope of the reaction, *p*-chlorophenyl (**1e**), *p*-fluoro (**1d**), *o*-methoxy(**1b**) and *p*-methyl- (**1c**) analogues of  $\alpha$ -diazoketones (Scheme 2a) were selected. Under the standard reaction conditions, using activated

tin,<sup>5</sup> all the  $\alpha$ -diazoketones yielded the corresponding 1-bromo-2-aryl-pent-4-en-2-ol derivatives when allyl bromide (**2**) was used (Table 1, entries 2–5). To evaluate the application of this protocol for aliphatic substrates and its tolerance of functional groups, we also used Cbz-protected L-

proline diazoketone (**1f**), and found that application of the standard reaction conditions produced the required product (**3f**) in good yield with a diastereomeric ratio of 2.2:1.0, as determined by <sup>1</sup>H NMR analysis of the crude product (Scheme 2b, Table 1, entry 6). The above reaction with clean

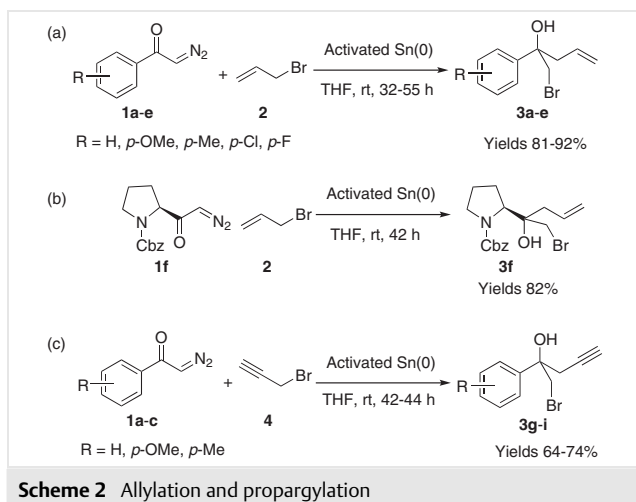
**Table 1** Allylation/Propargylation of  $\alpha$ -Diazoketones<sup>a</sup>

Entry	$\alpha$ -Diazoketone	Allyl bromide/propargyl bromide	Product	Time (h)	Yield (%) <sup>b</sup>
1				32	92
2				36	88
3				48	94
4				52	82
5				55	81
6 <sup>c</sup>				42	82
7				44	74
8				42	72
9				44	64

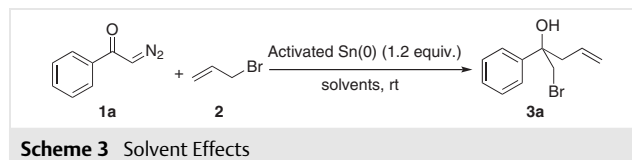
<sup>a</sup> All reactions were performed at room temperature, and monitored by TLC. All diazo compounds were prepared using a reported procedure. THF was used as a solvent for all the reactions. Activated tin was prepared from reduction of SnO with sodium stannite (Na<sub>2</sub>SnO<sub>2</sub>) using a reported procedure;<sup>5</sup> the reaction was unsuccessful when commercial tin was used.

<sup>b</sup> Isolated yield after purification.

<sup>c</sup> Diastereomeric ratio of the crude product was 2.2:1.0 determined by <sup>1</sup>H NMR spectroscopic analysis.



product formation demonstrated that the Cbz protecting group is well tolerated under the optimized conditions. Possible by-product formation from  $\alpha$ -diazoketones through Wolff rearrangement or carbene dimerization was ruled out as our reaction produced the allylated product with high selectivity and high yield. Screening of solvent (THF, diethyl ether, acetonitrile, and dichloromethane) to optimize the best solvent for allylation reaction demonstrated that THF produced the best results (Scheme 3, Table 2). As the reaction completed smoothly with high yield at room temperature, the effect of temperature was not assessed. However, when diazoacetophenone (**1a**) was treated with allyl bromide (**2**) in THF at 40 °C, the reaction was completed in 28 h to form 1-bromo-2-phenylpent-4-en-2-ol (**3a**) in 85% yield; as there was no reduction in the required time, we run all subsequent reactions at room temperature. The number of equivalents of tin was assessed using substrates **1a** and allyl bromide, and it was found that 1.2 equivalent of tin provided best yield; no improvement of rate of the reaction was observed when 2.0 equivalent of tin was used. It was found that activated zinc was also equally effective for this conversion, however, as our focus was on tin reagent, no further evaluation was undertaken with zinc or other metals. To utilize our optimized allylation of  $\alpha$ -diazoketones conditions to make propargylated product, substrates **1a-c** (Scheme 2c, Table 1, entries 7–9) were subjected to propargylation reaction using propargyl bromide and tin, and the corresponding propargylated products **3g-i** were obtained in moderate to high yield. Notably, electron-donating or electron-withdrawing groups did not have a significant effect on the reaction, as all substrates for allylation provided >80% yield, and no effort was made to study the electronic factors of diazo compounds. We focused on allyl bromide and propargyl bromide as these are commercially available, and therefore, substituted analogues of allyl and propargyl bromide were excluded from the present study.

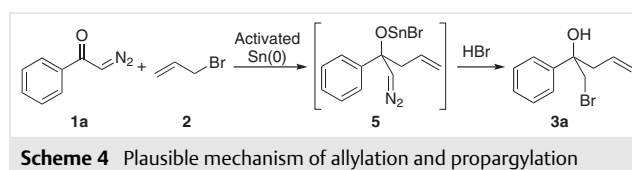


**Table 2** Solvent Screening of Reaction of Diazoacetophenone (**1**) with Allyl Bromide (**2**)<sup>a</sup>

Entry	Solvent	Time (h)	Yield (%) <sup>b</sup>
1	THF	32	92
2	CH <sub>2</sub> Cl <sub>2</sub>	32	82
3	CH <sub>3</sub> CN	32	83
4	Et <sub>2</sub> O	32	83

<sup>a</sup> All reactions were performed at room temperature and monitored by TLC.

<sup>b</sup> Isolated yield after purification.



A plausible mechanism is shown in Scheme 4.<sup>8</sup> The first step of the reaction is tin insertion to allyl bromide followed by 1,2-addition to the electrophilic carbonyl group of **1a** to form the active intermediate **5**. Intermediate **5** decomposes by extrusion of nitrogen to give active carbene, which reacts with HBr generated during work up process. No study was undertaken to prove the mechanism of the reaction, which was beyond the scope of the present research. The effectiveness of allylation/propargylation of  $\alpha$ -diazoketones using allyl/propargyltin bromide generated *in situ* from 1.2 equiv of tin and 1.5 equiv of allyl/propargyl bromide is reported in this manuscript.<sup>6,7</sup> As shown in Scheme 4, allylation of a carbonyl group with allyltin reagent generated a diazo intermediate, which undergoes extrusion of nitrogen to form a carbene that then reacts with HBr, which is generated in the reaction mixture, to produce the desired quaternary bromohydrin. In Table 1 we have shown that various  $\alpha$ -diazoketones react with allyl/propargyl tin bromide and the results clearly demonstrate that vast scope of this protocol.<sup>9</sup>

In conclusion, we have demonstrated that allylation/propargylation of  $\alpha$ -diazoketones using allyl/propargyl bromide and tin metal is an efficient protocol using less toxic tin metal to make 1-bromo-2-alkyl- or 2-arylpent-4-en-2-ols and 1-bromo-2-alkyl- or 2-arylpent-4-yn-2-ols. This protocol offers an alternative to the more expensive metal used for allylation and propargylation and is useful for gram-scale reactions. When 1.0 g of diazoacetophenone (**1a**) was subjected to our standard reaction conditions, 84%

yield of 1-bromo-2-phenylpent-4-en-2-ol (**3a**) was observed at room temperature. Therefore, this protocol is very useful to generate precursors for the construction of unique scaffolds for the drug discovery program, and as well as for accessing biologically active natural products.

### Conflict of Interest

The authors declare no conflict of interest.

### Funding Information

This research was self-funded by S.K.B., and S.K.B thanks SCC, Habra for providing facilities for this research.

### Acknowledgment

S.K.B. thanks the SCC, Habra, and S.J. thanks UTSA.

Samples of the tin-mediated allylation/propargylation described in this manuscript are available from the authors.

**Author Contributions:** Conceptualization S.K.B; validation, methodology, formal analysis, investigation, writing—original draft preparation, review and editing, S.K.B. and S.J. All authors have read and agreed to the published version of the manuscript.

### References and Notes

- (1) (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121. (c) Calter, M. A. *Curr. Org. Chem.* **1997**, *1*, 37.
- (2) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern catalytic methods for organic synthesis with diazo compounds*; Wiley-Interscience: New York, **1998**. (b) Davis, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075. (c) Doyle, M. P. *Metal Carbene Complexes in Organic Synthesis: Diazodecomposition - Insertion and Ylide Chemistry*, In *Comprehensive Organometallic Chemistry II, Vol. 12, Chap. 5.2*; Hegedus, L. S., Ed.; Pergamon Press: New York, **1995**. (d) Doyle, M. P. *Synthetic Carbene and Nitrene Chemistry*, In *Contemporary Reactive Intermediate Chemistry*; Moss, R. A.; Platz, M. S.; Jones, M. Jr., Ed.; John Wiley & Sons Inc: New York, **2004**. (e) Yates, P.; Farnum, D. G. *J. Am. Chem. Soc.* **1963**, *85*, 2967.
- (3) (a) Phil, H. L. *Bull. Korean Chem. Soc.* **2007**, *28*, 17. (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (c) Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Sadasiv, K.; Chary, Ch. J. *Chem. Lett.* **2003**, 248. (d) Yadav, J. S.; Reddy, B. V. S.; Biswas, S. K.; Sengupta, S.; Vishnumurthy, P. *Tetrahedron Lett.* **2008**, *49*, 1034.
- (4) (a) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347. (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. S.; Reddy, K. B. *Tetrahedron Lett.* **2002**, *43*, 1549. (c) Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. *Tetrahedron Lett.* **2001**, *42*, 6385. (d) Yadav, J. S.; Anjaneyulu, S.; Ahmed, Md. M.; Reddy, B. V. S. *Tetrahedron Lett.* **2001**, *42*, 2557. (e) Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. *Synlett* **2001**, 1608.
- (5) Sinha, A. K.; Sil, A.; Sasmal, A. K.; Pradhan, M.; Pal, T. *New J. Chem.* **2015**, *39*, 1685.
- (6) (a) Yasuda, M.; Tsuchida, M.; Baba, A. *Chem. Commun.* **1998**, 563. (b) Yadav, J. S.; Reddy, B. V. S.; Vishnumurthy, P.; Biswas, S. K. *Tetrahedron Lett.* **2007**, *48*, 6641.
- (7) (a) Lin, M.-H.; Kuo, C.-K.; Lin, W.-C.; Huang, Y.-C.; Tsai, Y.-T.; Liang, K.-Y.; Li, Y.-S.; Chuang, T.-H. *Tetrahedron* **2013**, *69*, 8263. (b) Fandrick, D. R.; Saha, J.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 5616.
- (8) Zheng, H.; Dong, K.; Wherritt, D.; Arman, H.; Doyle, M. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 13613.
- (9) **General procedure:** (-Diazoketone (1.00 mmol) and allyl bromide/propargyl bromide (1.50 mmol) were dissolved in THF (6.0 mL) at room temperature, then freshly activated tin metal<sup>5</sup> (1.20 mmol) was added (Table 1) and the reaction was monitored by TLC. Aqueous saturated ammonium chloride (10.0 mL) was used to quench the reaction, and extraction was performed with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (Merck, 100–200 mesh) using ethyl acetate and hexanes as eluent gave the desired product. <sup>1</sup>H and <sup>13</sup>C NMR spectra and other analytical data of compounds **3a–i** have been reported previously.<sup>6,7</sup>