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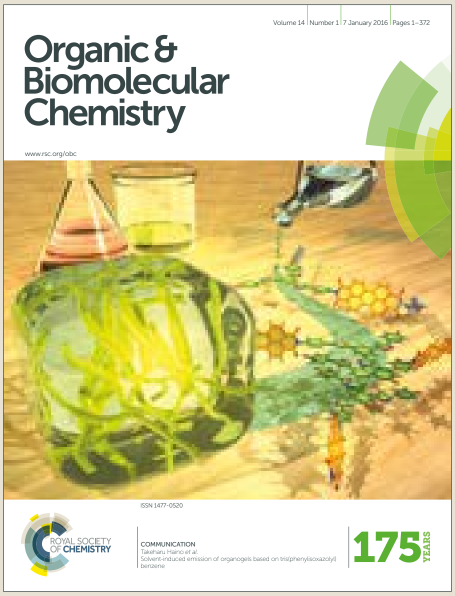

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Fe-catalyzed radical-type difunctionalization of styrenes with aliphatic aldehydes and trimethylsilyl azide via decarbonylative alkylation-azidation cascade

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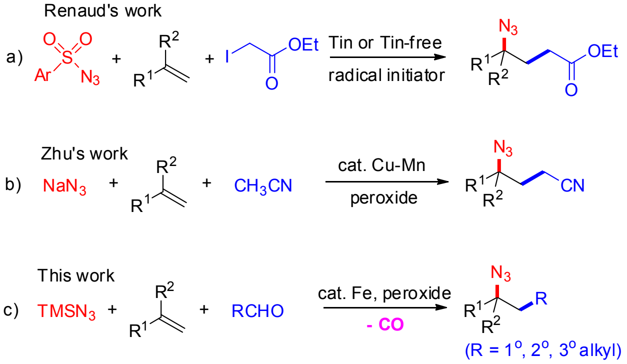
A convenient Fe-catalyzed decarbonylative alkylation-azidation cascade reaction of styrene derivatives with aliphatic aldehydes and TMSN$_3$ to provide aliphatic azides is developed. With DTBP as an oxidant and radical-initiator, this reaction smoothly converts aliphatic aldehydes into 1°, 2° and 3° alkyl radicals and subsequently allows for the cascade construction of C(sp^3)-C(sp^3) and C(sp^3)-N bonds via radical insertion and nucleophilic azidation.

Organic azides have been demonstrated as important molecules not only due to their remarkable biological activities, thus widely incorporated into lead compounds design in drug discovery; [1] but also for their synthetic versatility, as powerful precursors for a great number of nitrogen-containing species. [2] Moreover, organic azides are popular linkers, due to the mild and versatile copper-catalyzed "Click" chemistry with alkynes, surging at the interface between chemistry, medicine and biology.[3] Thus, the development of efficient synthetic methods for various organic azides is an ongoing interest for chemists.

With regard to the synthesis of aliphatic azides, classic methods rely on nucleophilic substitution/addition reactions of azide anion (or its precursors) to electrophilic substrates. In recent years, the direct difunctionalization of alkenes has become a powerful strategy in organic synthesis, which has also been applied to the preparation of aliphatic azides, to enable the direct installation of an azido group and introduction of another functionalities cross the C=C bond at one time to increase molecular complexity. [4] In this context, elegant work such as amino-azidation,[5] oxyazidation,[6] azido-trifluoromethylation,[7] azido-cyanation[8] and di-azidation[9] using different azido soucres (NaN$_3$, TMSN$_3$ or azidoiodine(III) reagents) has been realized. The alkylative azidation of alkene is important as it extends the carbon chain while introduces the azido group. However, the report on alkylative azidation of alkene is rare, especially for installation of an alkyl group to the terminal C=C bond to provide liner aliphatic azides. In this regard, an elegant method with ethoxyl iodoacetate and arylsulfonyl azide as the alkyl and azido source respectively, was developed by Renaud group, [10] which can proceed both with and without the assistance of organotin reagents. Very recently, a copper-catalyzed alkylative azidation of terminal alkenes with acetonitrile and NaN$_3$ was reported by Zhu and co-workers, [11] where acetonitrile was applied as a cheap and readily available source for the cyanomethyl group. However, these two precedents could not be applied for the introduction of ordinary liner or branched alkyl groups.



Scheme 1. Alkylative azidation of alkenes.

On the other hand, aldehydes are cheap and readily available chemicals and have been directly used for decarbonylative couplings catalyzed by ruthenium or rhodium, as shown by the extensive studies of C.-J. Li since 2009. [12] In contrast, we are interested in the metal-free decarbonylative reactions of aldehydes, with peroxides as radical initiator and oxidant.[13] The oxidative decarbonylative couplings of aldehydes with arenes,[13a] heteroarenes,[13b] styrene derivatives,[13c, 13d] and a cascade alkylation-cyclization of

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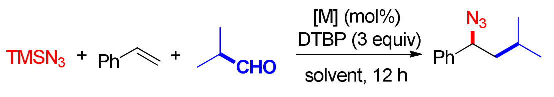
acrylamides[13e] were successively developed by our group. These decarbonylative reactions were further updated by other groups, with dioxygen as the radical initiator and oxidant.[14] Similarly, the radical type decarbonylative alkylations of aldehydes with C=C and C≡C were developed by Z.-P. Li[15a] , J.-H. Li[15b] and Pan[15c]. For the mechanism of these radical type decarbonylative reactions, it's widely accepted that an aliphatic aldehyde was transformed into an acyl radical, and the corresponding alkyl radical after spontaneous decarbonylation, [13-15] which inserted into the C=C bond to install an alkyl group and generate another carbon radical. Thus, we postulated that the combination of radical type decarbonylation of aliphatic aldehydes and various azidation reactions should provide a feasible method for the alkylation-azidation cascade difunctionalization of alkenes. Herein, we report a novel three-component oxidative decarbonylative alkylation-azidation cascade reaction of styrene derivatives with aliphatic aldehydes and trimethylsilyl azide ($TMSN_3$).

Table 1. Optimization of the oxidative decarbonylative alkylation-azidation [a]



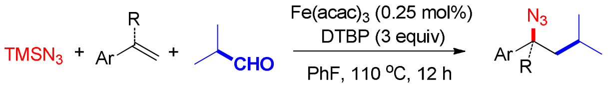
1a **2a** **3a**

entry	[M] (mol%)	Solvent	Temp. (°C)	yield [%][b]
1	$FeCl_2$ (10)	DCM	110	57
2	$FeCl_3$ (10)	DCM	110	55
3	$Fe(OAc)_2·4H_2O$ (10)	DCM	110	38
4	$Fe(acac)_3$ (10)	DCM	110	74
5	$Co(acac)_3$ (10)	DCM	110	<2
6	$Mn(OAc)_2$ (10)	DCM	110	<2
7	$Cu(OAc)_2$ (10)	DCM	110	51
8	$AgNO_3$ (10)	DCM	110	17
9	$Fe(acac)_3$ (1)	DCM	110	77
10	$Fe(acac)_3$ (0.25)	DCM	110	80
11 [c]	$Fe(acac)_3$ (0.25)	DCM	110	81
12 [c]	$Fe(acac)_3$ (0.25)	Toluene	110	75
13 [c]	$Fe(acac)_3$ (0.25)	PhCl	110	71
14 [c]	**$Fe(acac)_3$ (0.25)**	**PhF**	**110**	**84**
15 [c]	$Fe(acac)_3$ (0.25)	CH_3CN	110	68

[a] Conditions: styrene (**1a**, 0.2 mmol), isobutyraledhyde (**2a**, 3 equiv, 0.6 mmol), $TMSN_3$ (2 equiv, 0.4 mmol), [M] (metal catalyst, mol%), DTBP (3 equiv) and solvent (1 mL) were reacted at 110 °C for 12 h under air atmosphere unless otherwise noted. For precise weighting, a solution of $Fe(acac)_3$ in organic solvent was prepared and used. [b] Isolated yields. [c] Argon atmosphere.

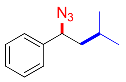
Based on our recent study [13d] and the above mechanistic analysis, styrene (**1a**), isobutyraldehyde (**2a**) and $TMSN_3$ were chosen as the model substrates. When di-*tert*-butyl peroxide (DTBP) was used as the oxidant and radical initiator, the desired alkylation-azidation product **3a** was isolated in 57% yield with 10 mol% $FeCl_2$ as the catalyst (Table 1, entry 1). Other iron species such as $FeCl_3$, $Fe(OAc)_2·4H_2O$ and $Fe(acac)_3$ were also effective catalysts for this cascade reaction, and $Fe(acac)_3$ provided the highest yield (74%, entry 4). Besides iron species, other transition-metal such as $Co(acac)_3$ and $Mn(OAc)_2$ were almost invalid for this reaction (entries 5 and 6), while $Cu(OAc)_2$ and $AgNO_3$ were reactive but resulted in lower yields (entries 7 and 8). Unexpectedly, the yield could be raised gradually from 74 to 80% by decreasing the loading of iron catalyst from 10 to 0.25 mol%, respectively (entries 3, 9 and 10), which might indicate that a low loading of $Fe(acac)_3$ as catalyst was able to control the homolytic cleavage rate of DTBP to match the rate of subsequent cascade reaction. By running this reaction under argon atmosphere instead of air, a slightly better yield of 81% was obtained (entry 11). Next, the solvent effect for this cascade reaction was evaluated. Low polarity solvents including toluene, DCM (dichloromethane), chlorobenzene (PhCl), fluorobenzene (PhF) and much more polar acetonitrile all turned out to be suitable, and fluorobenzene provided the best result among these solvents tested. (See supporting information for more detailed optimization.)

Table 2. Scope of the styrene derivatives on the oxidative decarbonylative alkylation-azidation [a]

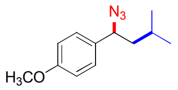


1a-1n **2a** **3a-3n**

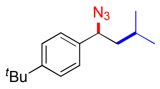
1a	styrene	**1b**	4-methoxylstyrene
1c	4-*tert*-butylsryrene	**1d**	4-methylstyrene
1e	4-chloromethylstyrene	**1f**	4-tirfluoromethylstyrene
1g	4-fluorostyrene	**1h**	4-chlorostyrene
1i	4-boromostyrene	**1j**	2-chlorostyrene
1k	3-chlorostyrene	**1l**	3-boromostyrene
1m	α-methylstyrene	**1n**	1,1-diphenylethene
1o	4-nitrostyrene		



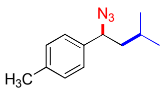
3a, 84%



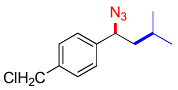
3b, 68%



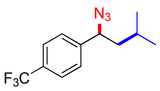
3c, 75%



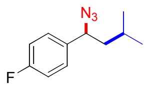
3d, 78%



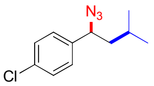
3e, 71%



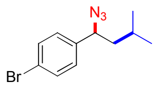
3f,61%



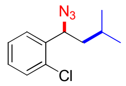
3g, 83%



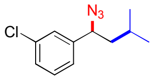
3h, 71%



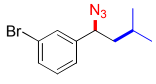
3i, 67%



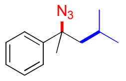
3j, 78%



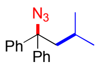
3k, 76%



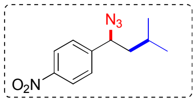
3l, 75%



3m, 75%



3n, 76%



N. D.

[a] Conditions: alkene (**1a-1m**, 0.2 mmol), isobutyraledhyde (**2a**, 3 equiv, 0.6 mmol), $TMSN_3$ (2 equiv, 0.4 mmol), DTBP (3 equiv) and $Fe(acac)_3$ (0.25

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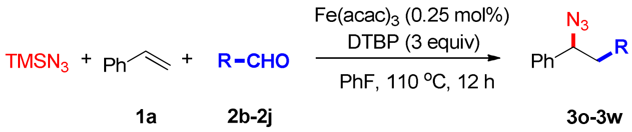
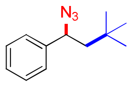
mol%) in fluorobenzene (1 mL, pre-prepared solution) were reacted at 110 °C for 12 h under argon atmosphere. Isolated yields. N.D. = not detected.

The generality and limitation of this decarbonylative alkylation-azidation of styrene derivatives, aliphatic aldehydes and $TMSN_3$ was subsequently investigated. The effect of substituents on the styrene moiety is listed in Table 2. Various styrene derivatives bearing electron donating or withdrawing substituents on the phenyl moiety (**1a**-**1n**) smoothly underwent there-component radical type cascade reaction to afford the desired alkylated azides in moderate to good yields, such as methoxy (**1b**), *tert*-butyl (**1c**), methyl (**1d**) chloromethyl (**1e**), trifluoromethyl (**1f**) and halo (**1g**-**1k**); but 4-nitrostyrene (**1o**) failed in this reaction. The optimized reaction condition could be applied to the styrene derivatives with chloro substituted at *para*, *meta* and *ortho* position (**1h**, **1k** and **1j**), and similar yields were obtained. Besides mono-substituted terminal alkenes, the di-substituted terminal alkenes α-methylstyrene (**1m**) and 1,2-diphenylethene (**1n**) also were suitable substrates and can be transformed into the corresponding products **3m** and **3n** in 75 and 76% yields, respectively. It's encouraged that this alkylation-azidation cadcade reaction could incorporate chloromethyl group (**1e**) into the product directly, considering that an benzyl chloride functional group would be highly reactive for nucleophilic substitution/addition reaction, thus product **3e** could not be prepared by classic nucleophilic substitution from NaN_3.

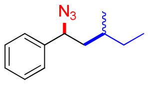
Table 3. Scope of the aliphatic aldehydes on the oxidative decarbonylative alkylation-azidation [a]



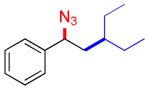
2b	pivaldehyde	**2c**	2-methylbutanal
2d	2-ethylbutanal	**2e**	2-methylpentanal
2f	2-ethylhexanal	**2g**	cyclohexanecarbaldehyde
2h	cyclopetanecarbaldehyde	**2i**	cyclohex-3-enecarbaldehyde
2j	2-phenylacetaldehyde		



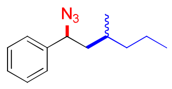
3o, 84%



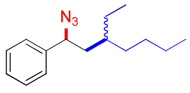
3p, 78%[b]



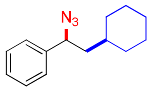
3q, 68%



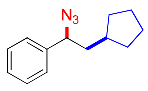
3r, 73%[b]



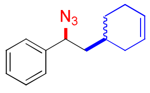
3s, 67%[b]



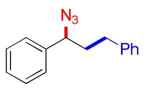
3t, 64%



3u, 65%



3v, 75%[b]

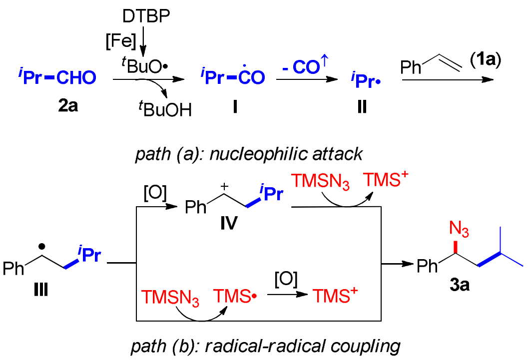


3w, 55%

[a] Conditions: styrene (**1a**, 0.2 mmol), aldehyde (**2b-2j**, 3 equiv, 0.6 mmol), $TMSN_3$ (2 equiv, 0.4 mmol), DTBP (3 equiv) and $Fe(acac)_3$ (0.25 mol%) in fluorobenzene (1 mL, pre-prepared solution) were reacted at 110 °C for 12 h under argon atmosphere. Isolated yields. [b] d.r. = 1:1 (as roughly determined by GC).

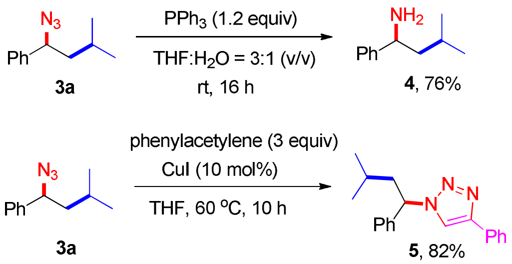
After investigating the scope of styrene derivatives, we next tested the generality of this cascade reaction of styrene (**1a**) with different aliphatic aldehydes (**2b**-**2j**) under the optimized conditions (Table 3). While the α-di-substituted pivaldehyde (**2b**) provided a tertiary carbon radical after decarbonylation, the α-mono-substituted aliphatic aldehydes including 2-methylbutanal (**2c**), 2-methylpentanal (**2d**), 3-ethylbutanal (**2e**), 2-ethylhexanal (**2f**), cyclohexanecarbaldehyde (**2g**), cyclopentanecarbaldehyde (**2h**) and cyclohex-3-enecarbaldehyde (**2i**) would provide secondary carbon radicals. Similarly, α-unsubstituted aliphatic aldehyde 2-phenylacetaldehyde (**2j**) would provide a primary carbon radical after oxidative decarbonylation. Gratifyingly, all of these aliphatic aldehydes underwent alkylation-azidation cascade reaction with styrene and $TMSN_3$ to yield the targeted azides smoothly. Among them, liner aliphatic aldehyde (**2j**) provided a lower yield of 55%, which might be caused by the relatively severer self-aldol condensation. It's delighted that the cyclohex-3-enecarbaldehyde (**2i**) turned out to be a good substrate for this cascade reaction, and the internal C=C bond caused little influence for the difunctionalization of styrene, which demonstrated nice chemo selectivity of this reaction.

Based on the literature reports [14, 15], radical capturing experiments (see ESI), and our previous studies,[13] a plausible mechanism to understand this three-component decarbonylative alkylation-azidation cascade reaction was proposed, with the reaction of styrene (**1a**), isobutyraldehydes (**2a**) and $TMSN_3$ as an example (Scheme 2). First, the homolytic cleavage of DTBP is accelerated by iron catalyst to form *tert*-butoxy radical. [16] Subsequent hydrogen atom abstraction of the aldehyde (**2a**), spontaneous decarbonylation and insertion into the C=C bond of styrene (**1a**) to afford a benzyl radical **III**. Next, there are two possible pathways for the C-N bond formation. In path (a), the benzyl radical **III** is oxidized to provide a benzyl cation **IV**,[4a, 11] and the nucleophilic attack by azide anion (from $TMSN_3$) [4a, 11] realizes the C-N bond formation. Alternatively, in path (b), the direct radical-radical coupling of the benzyl radical **III** and azido radical (also from $TMSN_3$) [10e] furnishes the product and a TMS radical, which would be further oxidized into TMS cation and converted to TMS-O^{t}Bu ultimately. Although path (b) can't be excluded at this stage, path (a) is considered as the predominant pathway because of the relatively strong oxidative reaction conditions and good stability of benzyl cation **IV**.



Scheme 2. Proposed mechanism for the cascade reaction.

It is important to note that these alkylated azides can be easily subjected to further chemical manipulations as depicted in Scheme 3. The Staudinger reaction of azide **3a** and PPh_3 in aqueous THF provided the α-substituted benzyl amine **4**, while the "Click" reaction of azide **3a** and phenylactylene assisted by a catalytic amount of CuI produced triazole **5** smoothly.



Scheme 3. Synthetic applications of the alkylated azides.

Conclusions

We have developed a convenient iron-catalyzed three-component decarbonylative alkylation-azidation of styrene derivatives with aliphatic aldehydes and $TMSN_3$ to provide aliphatic azides. With DTBP as an oxidant and radical-initiator, this reaction efficiently converted readily available liner, α-mono-substituted and α-di-substituted aliphatic aldehydes into primary, secondary and tertiary alkyl radicals for the cascade construction of C(sp^3)-C(sp^3) and C(sp^3)-N bonds. The cheap and readily availability of styrenes and aliphatic aldehydes, simple reaction conditions, wide substrate scope and versatile synthetic utilities of aliphatic azides, would render this alkylation-azidation cascade reaction attractive for organic synthesis and medicinal chemistry.

Acknowledgments

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The authors declare no competing financial interest.

Notes and references

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Abstract for the Contents Pages

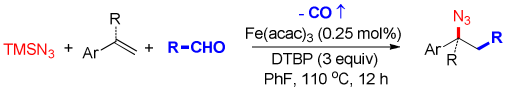
Fe-catalyzed radical-type difunctionalization of styrenes with aliphatic aldehydes and trimethylsilyl azide via decarbonylative alkylation-azidation cascade

Wei-Yu Li, Qi-Qiang Wang and Luo Yang*

Text:

A three-component oxidative decarbonylative alkylation-azidation cascade reaction of styrene derivatives with aliphatic aldehydes and $TMSN_3$ to provide aliphatic azides is developed.

Graphic:



Advantages:

- abundant aliphatic aldehyde as 1°, 2° and 3° alkyl source
- cascade formation of $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-N via radical insertion and nucleophilic azidation
- 24 examples and up to 84 % yield