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Oxidative Radical Addition−Cyclization of Sulfonyl Hydrazones with Simple Olefins by Binary Acid Catalysis

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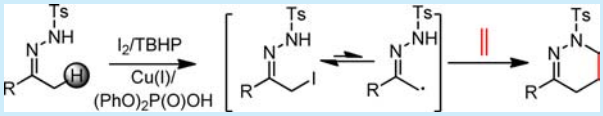
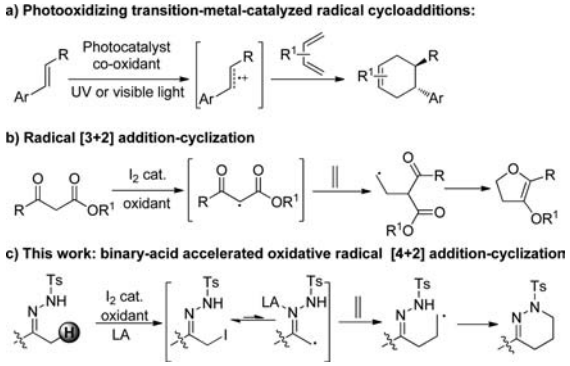
Supporting Information

ABSTRACT: An unprecedented binary acid accelerated oxidative radical annulation of sulfonyl hydrazones with simple olefins is described. Notably, this method provides a novel oxidative radical cycloaddition for the construction of six-member heterocycles. It offers a rapid and efficient approach to tetrahydropyridazines which are key structural motifs in pharmaceutically active compounds.



As a member of the most important class of transformations in organic synthesis, cycloaddition reactions, such as Diels−Alder reactions, provide a convenient way to construct versatile heterocyclic compounds.[1] Over the past several years, radical cycloaddition reactions have attracted considerable attention. The radical cations generated by photocatalysts through single electron transfer were recently employed in these [4 + 2] cycloaddition processes (Scheme 1a).[2] On the other hand, atom transfer radical cyclization reactions, which involve the transfer of a halogen atom (X = I, Br, or Cl) from one carbon center to olefins, tend to form five cyclic compounds or polymerize.[3] However, very few examples of a [4 + 2] radical addition−cyclization reaction were reported.[4] Hence, achieving a catalytic oxidative [4 + 2] radical addition−cyclization reaction with simple olefins remains elusive, despite the notable advances in [4 + 2] oxidative cycloaddition through C−H activation.[5−7]

Scheme 1. Radical Cycloaddition Reaction



In the past decade, I_2 as a high efficiency catalyst has achieved a number of direct oxidative C(sp^3)−H functionalizations to form C−X (X = O, N) bond compounds via in situ generated α-C(sp^3)−I intermediates.[8,9] In elegant recent studies, Lei and co-workers found that iodine could catalyze radical oxidative β-keto esters with alkenes and alkynes to give five-member annulations of dihydrofurans and furans (Scheme 1b).[10] However, such radical addition−cyclization leading to six-membered rings has not been achieved so far, as usually encountered in radical-type cyclizations. Tetrahydropyridazines are versatile structural motifs in a number of pharmaceutically active compounds, and few general methods are applied in their synthesis.[11−13] Recently, we have pursued an oxidative radical coupling between ketone hydrazone and simple alkenes, providing arguably the most straightforward and atom economic pathway toward tetrahydropyridazines. This radical [4 + 2] cycloaddition approach is conceivably challenging when considering that hydrazones, such as *N*-tosylhydrazones, tend to form *N*-radicals, which were known to undergo five-membered cyclization reactions.[14−17] In addition, the stability of alkenes under the oxidative conditions would also be of concern, particularly in an intermolecular context. Herein, we report a distinctive Lewis acid/I_2 cocatalytic strategy for the oxidative radical addition−cyclization reaction of sulfonyl hydrazones and alkenes. A binary acid catalyst involving a copper Lewis acid and phosphoric acid[18,19] was identified to facilitate the crucial radical addition and cyclization step and meanwhile suppress the possible degradation and polymerization of alkenes (Scheme 1c).

Oxidative [4 + 2] cycloaddition of *N*-tosylhydrazone **2a** with styrene **3a** was chosen as a model reaction. The use of typical oxidative conditions led to no desired product (e.g., Table 1, entry 2). Unexpectedly, we found that the use of our binary acid conditions could promote effective production of the desired adduct **4a**. Eventually, we were able to identify a viable complex composed of $Cu(CH_3CN)_4BF_4$ and diphenyl phosphate **1**. In the presence of Cu/**1** (5 mol %), the desired [4 + 2] cycloadduct **4a** can be obtained in 76% yield (Table 1, entry 1 vs 2). In the

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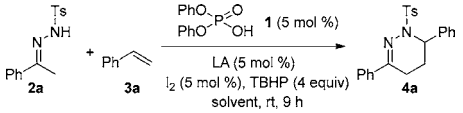
Table 1. Influence of Reaction Parameters on the Catalytic Oxidative [4 + 2] Cycloaddition of *N*-Tosylhydrazones 2a and Styrene 3a[a]



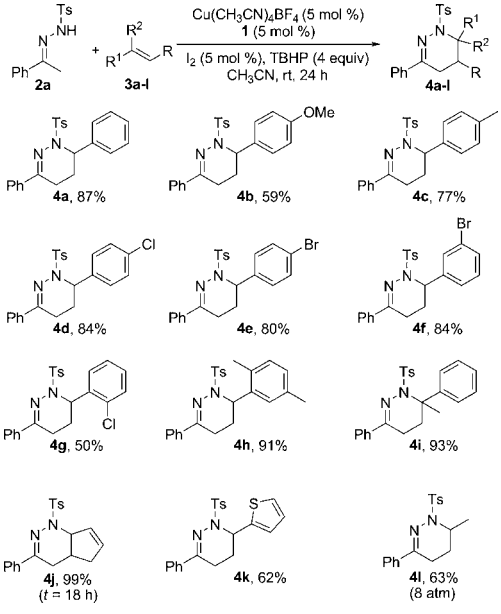
entry	catalyst	solvent	yield (%)[b]
1	$Cu(CH_3CN)_4BF_4$/**1**	CH_3CN	76
2	none	CH_3CN	trace
3	$Cu(CH_3CN)_4BF_4$	CH_3CN	33
4	**1**	CH_3CN	trace
5	HBF_4	CH_3CN	NR
6[c]	$Cu(CH_3CN)_4BF_4$/**1**	CH_3CN	75
7[d]	$Cu(CH_3CN)_4BF_4$/**1**	CH_3CN	87

[a]General conditions: $Cu(CH_3CN)_4BF_4$ (5 mol %), **1** (5 mol %), I_2 (5 mol %), TBHP (0.8 mmol), **2a** (0.2 mmol), and **3a** (1.0 mmol) at room temperature. [b]Determined by ^1H NMR analysis with an internal standard, 1,3,5-trimethyloxylbenzene. [c]Reaction was carried out in the dark. [d]t = 24 h. NR = No reaction.

presence of diphenyl phosphate **1**, other metal cocatalysts (such as Cu^{II}, In^{III}, Mg^{II}, Zn^{II}, Fe^{III}, Fe^{II}, and so on) were less effective under these conditions (<20% yield, Table S1). In control experiments, the use of either $Cu(CH_3CN)_4BF_4$ (33% yield, Table 1, entry 3) or **1** alone (Table 1, entry 4) was ineffective, highlighting the critical role of the binary acid. The possible effect of a strong Brønsted acid could also be excluded, as the reaction in the presence of HBF_4 only did not work at all (Table 1, entry 5). The reaction was also applied in the dark to give a similar yield, excluding the possible photocatalysis (Table 1, entry 1 vs 6). The yield could be slightly improved by extending the reaction time (Table 1, entry 7 vs 1).

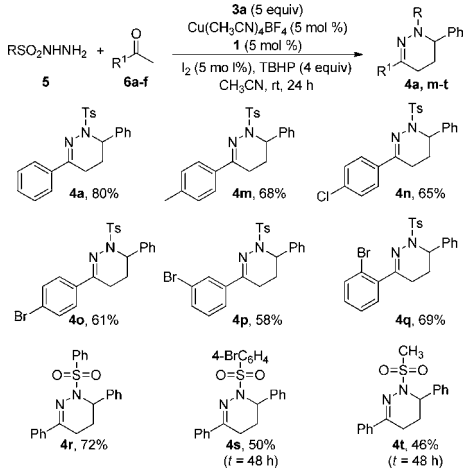
With optimized conditions established, we next explored the substrate scope. As shown in Scheme 2, an array of simple alkenes **3a–l** was tested, resulting in the expected tetrahydropyridazines **4a–l** in moderate to excellent yields. Various styrenes **3a–h** could be well applied in the reaction, and 1,1-disubstituted α-methylstyrene **3i** and heteroaromatic 2-vinylthiophene **3k** were also tolerated. Moreover, cyclopentadiene **3j** worked well to give the desired adducts **4j** with excellent yield and diastereoselectivity. In addition, an aliphatic alkene, propene **3l**, also worked leading to a 63% yield.

Scheme 2. Substrate Scopes for Simple Alkenes



Following the success of the formation of tetrahydropyridazines from alkenes **3** and *N*-tosylhydrazones **2a**, we explored the possibility of performing a one-pot three-component transformation of styrene **3a**, sulfonyl hydrazines **5**, and arylethanones **6a–f**. In this process, the hydrazones would be generated *in situ*. As can be seen, electron-rich and -deficient acetophenones gave similar results (**4m–q**). Unfortunately, the reaction did not work with heteroarylethanones and alkylethanones such as acetone, or methyl acetoacetate. Finally, different sulfonyl hydrazines **5b–d** were tested, demonstrating similar performance (**4r–s**). It was worth mentioning that alkyl sulfonyl hydrazide **5d** could afford the desired product **4t** in moderate 46% yield (Scheme 3).

Scheme 3. Substrate Scopes for Sulfonyl Hydrazines under One-Pot Reaction Conditions



To probe the mechanism of this oxidative annulation process, different kinds of iodine sources were examined in the model reaction (Table S2). In the absence of an iodine source, no reaction was observed. When the widely used iodide source such as KI and *n*-Bu_4NI was used, no desired product was observed. However, *N*-iodosuccinimide (NIS) displayed reactivity similar to that of I_2. Stoichiometric experiments were then carried out to look into the nature of the iodine catalysis (Scheme 4 and Supporting Information (SI)). Iodine was found to react with hydrazine **2a** quickly to afford iodinated adduct **C-2a**/**N-2a** in the absence of *tert*-butyl hydroperoxide (TBHP). The C-iodide and N-iodide ratio was determined to be 1:2 (Scheme 4A). The addition of TBHP could transform the mixture containing both **N-2a** and **C-2a** to a single C-iodinated product **C-2a** along with a tosyl shifted product **7** (**C-2a**/**7** = 5:1). Separate experiments between **2a** and iodine in the presence of TBHP further affirmed the sole formation of **C-2a** (Scheme 4B), and the conversion was completed in 3 h with a significant amount of **7** being also detected. When the thus formed **C-2a** mixture was treated with styrene **3a** in the presence of Cu/**1**, smooth conversion to the desired cycloadduct was observed and the desired product was isolated in 41% yield. In sharp contrast, no reaction was observed in the absence of a binary acid (Scheme 4C). Taken together, these experimental observations indicated C-iodinated adduct **C-**

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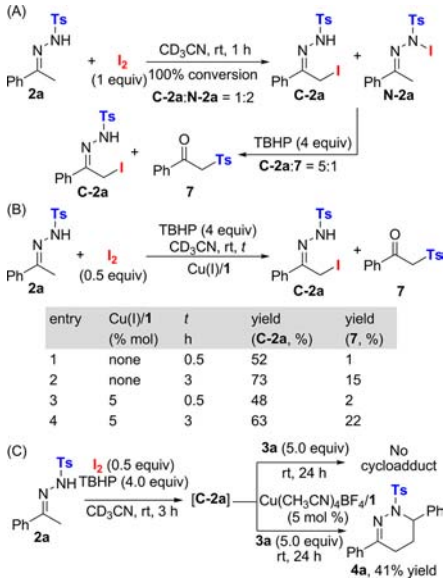
Scheme 4. Study of Stoichiometric Reaction between *N*-Tosylhydrazone 2a and I_2



entry	Cu(I)/1 (% mol)	t h	yield (C-2a, %)	yield (7, %)
1	none	0.5	52	1
2	none	3	73	15
3	5	0.5	48	2
4	5	3	63	22

2a is likely a key intermediate in the reaction and the binary acid plays a critical role in promoting the coupling of **C-2a** and styrene. As also revealed in Scheme 4B, the binary acid showed no effect in the iodination step.

To define the roles of binary acid $Cu(CH_3CN)_4BF_4$/**1**, kinetic studies were carried out by monitoring the reactions by using *in situ* IR. *N*-Sulfonylhydrazone **2a** could be easily oxidized through I_2/TBHP to form **C-2a** in 10 min even in the absence of a binary acid (Figure 1A), suggesting that the binary acid Cu^I/**1** did not participate in this step. In comparison, the promoting effect of binary acid Cu^I/**1** in the reaction was clearly noted with the formation of **4a** dramatically accelerated in the presence of Cu^I/**1** (Figure 1B). *In situ* monitoring of the reaction by ^{1}H NMR also revealed the quick formation of C-iodinated adducts **C-2a**

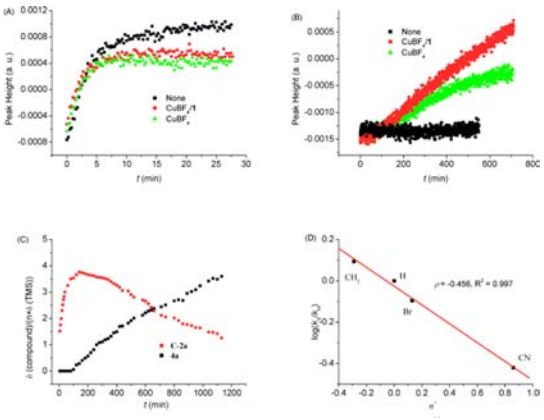
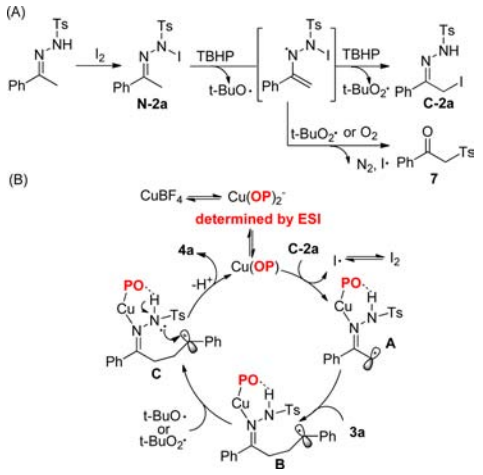


Figure 1. (A) Kinetics of the stoichiometric reactions of *N*-tosylhydrazone **2a** and I_2 in the presence of TBHP and acid catalysts in CH_3CN monitored by in situ IR at 1269 cm^{-1} (**C-2a-I**) at room temperature (see SI). (B) Kinetics of the oxidative cycloaddition reactions monitored by in situ IR at 895 cm^{-1} (adduct **4a**) at room temperature. (C) In situ monitoring oxidative cycloaddition reaction by ^{1}H NMR at 4.13 ppm (adduct C-**2a**) and 5.60 ppm (adduct **4a**) at room temperature. (D) Hammett plot of oxidative [4 + 2] cycloaddition of *N*-tosylhydrazone **2a** and substituted styrenes **3**.

(Figure 1C). There seemed also an induction time for the formation of the desired product **4a**, corresponding to the period of **C-2a** formation. After the induction period, the steady formation of **4a** along with the decrease of **C-2a** could be clearly noted by ^{1}H NMR. These observations verified that **C-2a** was the key reactive intermediate for the reaction. A control experiment in the presence of TEMPO, a typical radical quencher, showed no reaction under otherwise identical conditions, suggesting the coupling of **C-2a** and styrene would be of a free radical nature. Moreover, a radical clock vinyl-cyclopropane was tested under the reaction conditions. Though the desired product was not obtained, ring opening of the cyclopropyl moiety was observed to form allyl sulfone (see SI), verifying the radical nature of the reaction.

Based on the experimental observations, we proposed a radical addition/cyclization mechanism (Scheme 5). The co-action of

Scheme 5. Proposed Catalytic Cycle of Oxidative [4 + 2] Cycloaddition



iodine and TBHP first generates the C-iodinated **C-2a**, likely via an N-iodinated intermediate **N-2a**. The always isolated side product **7** adds support to this pathway. It also possible that **N-2a** and **C-2a** are competing products with the first being readily transferred to **C-2a** as experimentally verified. Under the acidic conditions, **C-2a** undergoes homolysis with the assistance of the binary acid Cu(I)/**1** complex, to give the key radical intermediate **A**. With the presence of the Cu(I) complex, a competing single electron transfer (SET) may also facilitate the generation of radical **A** and an iodide anion as known in atom transfer radical addition (ATRA) processes.[3] However, the inefficiency observed with the Cu(I) halide catalyst (Table S1, entry 2) disfavors the SET pathway. In addition, the generally applied mild reaction conditions are also in line with a facile C−I homolysis process, since ATRA with a copper complex normally require high temperature.[3c] That said, we were unable to completely rule out the SET process at this moment. Subsequently, irreversible radical addition of **A** to styrene and cyclization via intermediate **B** and **C** afford the final adduct **4a**. In this cycle, the critical roles of binary acid $Cu(CH_3CN)_4BF_4$/**1** lie in its complexation with the hydrazine moiety, as verified by NMR (SI, Figure S2), thus facilitating the homolysis as well as the following radical addition and cyclization. A Hammett plot was constructed to probe the electronic effects of the substrate alkene on the reaction rate (Figure 1D). The plot in Figure 1D revealed a negative, yet small ρ value (−0.456), which is consistent with the polar effect

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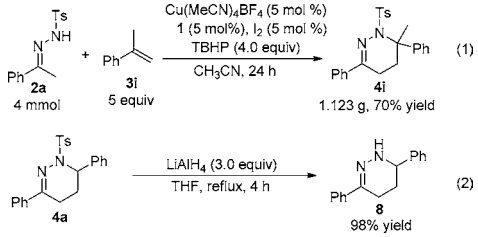
expected for the addition of an electrophilic carbon radical onto the alkene.[20]

The developed oxidative annulation could be performed on a gram scale, giving **4i** in 70% yield (eq 1). Alternatively, the *N*-sulfonyl group of **4a** could be easily removed by reduction to afford **8** in excellent yield (eq 2).[11c]



In summary, we have developed a distinctive oxidative radical [4 + 2] cycloaddition for the one-pot synthesis of tetrahydropyridazines from *N*-tosylhydrazones and simple alkenes. Notable features of this transformation include binary-acid catalysis in oxidative radical cyclization. Further extension of the methodology to other kinds of alkenes and investigations into a catalytic asymmetric version of this reaction are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01360.

General experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra, IR spectra and HRMS for new products (PDF)

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Notes

The authors declare no competing financial interest.

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