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Succinimide-Promoted Malonylamination of Alkenes with Amines and Iodonium Ylides via Trapping of Transient Aminium Radical Cations

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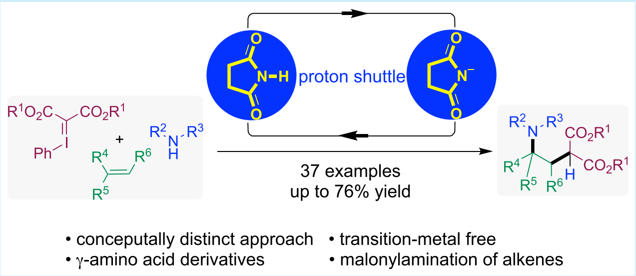
Supporting Information

ABSTRACT: A conceptually distinct strategy enabling malonylamination of alkenes with abundant amines and iodonium ylides without assistance of any transition metal was developed. Succinimide was identified as a proton shuttle that can not only largely accelerate the process of trapping highly unstable radical ion pairs with alkenes but also significantly improve the chemical yields.



Carboamination of alkenes has emerged as a streamlined strategy for the synthesis of functionalized amines that are fundamentally important in many research areas such as pharmaceuticals, agrochemicals, and materials science.[1] As a result, a diverse array of intramolecular,[2] two-component,[3] and three-component[4] carboamination of alkenes have been established. For these carboamination transformations, transition metals generally play an essential role in the bond-forming events while tailored amides, sulfamides, azides, or nitriles were used as the most frequent nitrogen sources, as these reagents are compatible with transition metals and external oxidants. Despite these important advances, direct carboamination of alkenes with simple amines in the absence of transition metals remains an unresolved problem.

Instead of exploiting the classical nucleophilic property of amines in the formation of carbon−nitrogen bonds, the generation of transient aminium radical cations via one-electron oxidation of amines would provide an alternative approach. However, the application of amines to a carboamination process via trapping of aminium radical cations remains elusive. The lack of this type of reaction is presumably attributed to the problem that the controllable one-electron oxidation of amines and subsequent trapping of transient aminium radical cations are generally not productive, as these highly unstable species could undergo fast transformations to give α-aminoalkyl radicals and iminium ions.[5−9] As a consequence, chemical bonds formed at carbon (adjacent to nitrogen) rather than direct bond formation at nitrogen. Though simple amine-mediated C−N bond formation through aminium radical cation intermediates is challenging, the research groups of Zheng and Knowles developed amination of alkenes with secondary amines through aminium radical cations addition of double bonds under a ruthenium or an iridium photoredox protocol (Figure 1a).[10,11]

Huang et al. discovered that an amine−I_2 charge-transfer complex could facilitate the inert C−N bond activation.[12] Recently, we found that the halogen-bonding complex between iodonium ylides and tertiary arylamines could induce a single-

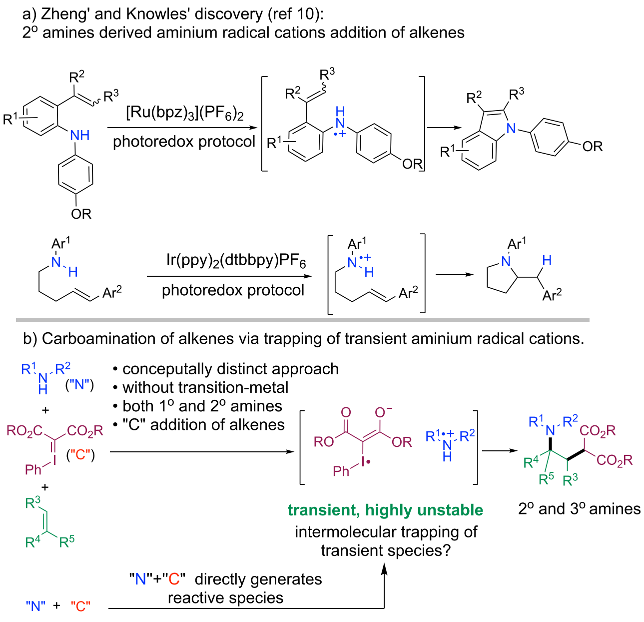


Figure 1. Generation and trapping of transient aminium radical cations.

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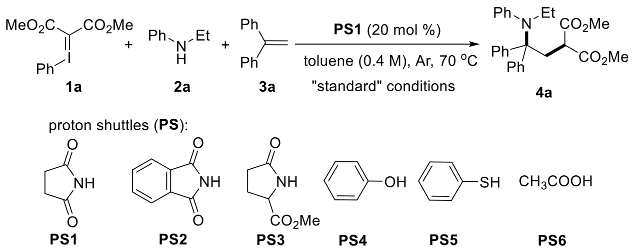
electron-transfer (SET) process, leading to the cyclization of tertiary arylamines via C−C bond formation.[13] Herein, we established a distinct approach to achieving a three-component malonylamination of alkenes with simple primary and secondary amines and iodonium ylides. In this transformation, C−N bond formation was realized via trapping of transient aminium radical cations. Thus, the simple merging of alkenes, carbon, and nitrogen sources together can directly lead to the desirable products (Figure 1b).

Initially, we screened a broad range of different additives including Brønsted bases and acids that can mediate the proton transfer process. The experimental results reveal that succinimide is an optimal choice. Using 20 mol % of succinimide **PS1** as a proton shuttle, the reaction of iodonium ylide **1a**, secondary arylamine **2a**, and alkene **3a** proceeded smoothly at 70 °C in toluene to give **4a** in 62% yield within only 20 min (Table 1, entry 1). In contrast, the reaction was much slower and the chemical yield of **4a** dropped dramatically without assistance of a proton shuttle (Table 1, entry 2). Similarly, using phthalimide **PS2** instead of **PS1** as a proton shuttle, nearly the same efficiency of this transformation was observed (Table 1, entry 3). However, using a less acidic amide **PS3** instead of **PS1**, no substantial effect on the reaction outcome was observed (Table 1, entry 4). The investigation of the other potential proton shuttles **PS4−5** reveals that this transformation could not be compatible with these acids (Table 1, entries 5−6). The pioneering work of Zhou and Zhu revealed that Brønsted acids could serve as excellent proton shuttles.[14] For this malonylamination process, no desirable product **4a** was obtained using a Brønsted acid, such as CH_3COOH, CF_3COOH et al., as a proton shuttle. The variation of temperature (Table 1, entries 8−11) and amount of succinimide (Table 1, entries 12−13) did not increase the chemical yield of product **4a**. Further screening of different solvents reveals that toluene is an optimal choice.

Table 1. Optimization of Reaction Conditions[a]

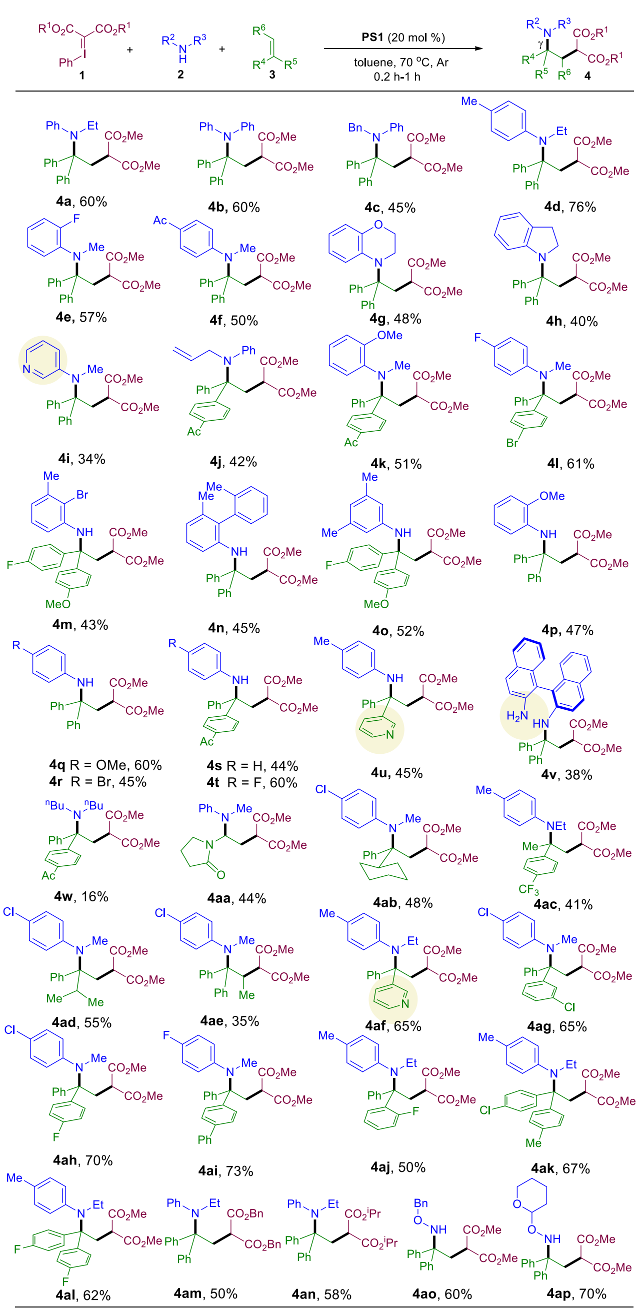


entry	variation from the “standard” conditions	time	yield (%)[b]
1	*none*	*0.3 h*	62
2	*without **PS1***	*4.0 h*	37
3	**PS2** instead of **PS1**	0.3 h	62
4	**PS3** instead of **PS1**	4.0 h	45
5	**PS4** instead of **PS1**	24 h	<5
6	**PS5** instead of **PS1**	24 h	<5
7	**PS6** instead of **PS1**	24 h	<5
8	at 80 °C	0.3 h	60
9	at 60 °C	1.0 h	59
10	at 40 °C	5.0 h	52
11	at rt	6.0 h	40
12	10 mol % **PS1**	1.0 h	56
13	30 mol % **PS1**	0.2 h	60
14	DCE instead of toluene	0.5 h	53
15	hexane instead of toluene	3.0 h	50
16	dioxane instead of toluene	1.5 h	34
17	DME instead of toluene	1.5 h	44

[a]Unless otherwise noted, all the reactions were carried out with **1a** (0.6 mmol), **2a** (0.45 mmol), **3a** (0.3 mmol), and **PS1** (20 mol %) in 0.75 mL of solvent as indicated at 70 °C. [b]Isolated yield.

Under the optimized reaction conditions, the substrate scope was investigated. As shown in Scheme 1, different amines, alkenes, and malonyl-type iodonium ylides were studied. The results reveal that both primary and secondary arylamines could be used as successful substrates. Regardless of the substitution position (i.e., ortho, meta, para), the functional

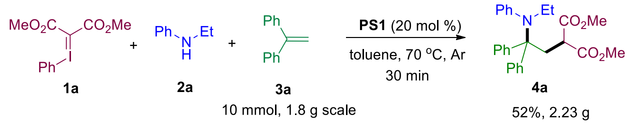
Scheme 1. Substrate Scope[a,b]



[a]Unless otherwise noted, all the reactions were carried out with **1** (0.6 mmol), **2** (0.45 mmol), **3** (0.3 mmol), and **PS1** (20 mol %) in 0.75 mL of toluene at 70 °C. [b]Isolated yield.

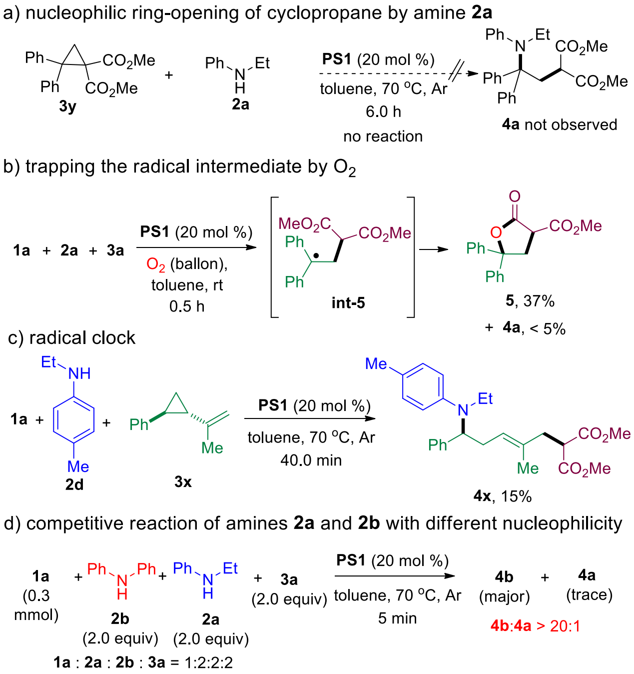
groups could be installed in different positions. Meanwhile, substitution groups with different electronic properties, such as electron-withdrawing, neutral, and electron-donating, were tolerated in this transformation. Arylamines bearing multi-substitutions were amendable to this malonylamination reaction. Cyclic arylamines, 3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine and indoline, were used as effective substrates to generate the desirable products (**4g** and **4h**). Significantly, the formation of the C−N bond was achieved by using a pyridine-base amine (**4i**) albeit with moderate chemical yields. 1,1′-Binaphthyl-2,2′-diamine was employed as an effective substrate to give product **4v**, indicating that the final product bearing the free amine group could be tolerated. An aliphatic amine such as dibutylamine was reactive in this transformation while low yield was obtained in this case (**4w**). Noteworthily, the problematic primary amines could be used as effective substrates in this carboamination process. This could be attributed to the highly steric hindrance of the generated secondary amines products, which prevents them from further oxidation by iodonium ylides. Then different alkenes were investigated. Aromatic rings of alkenes could be decorated with a diversified array of substitution groups with different electronic properties. Some of these alkenes allowed access to hindered amines, such as **4ad** and **4ae**. A pyridine-substituted alkene could be applicable to this transformation to give product **4af**. The structure of product **4al** was confirmed by single-crystal X-ray diffraction (CCDC 1881966). However, unactivated olefins, styrene, and stilbene could not be tolerated under the optimized reaction conditions. Further investigation of malonyl-type iodonium ylides indicates that different esters (i.e., Me, Bn, *i*Pr) were amendable to this reaction. Remarkably, hydroxylamines could also be used as effective reactants to give the desirable carboamination products **4ao** and **4ap** within several minutes. This carboamination transformation reaction was amendable to gram-scale synthesis. Upon using 1.8 g of **3a** (10 mmol) as starting material, the desirable product **4a** was obtained in 52% (2.23 g) yield (Scheme 2).

Scheme 2. Gram-Scale Synthesis



To provide some insight into this carboamination process, several experiments were carried out to investigate the reaction pathway (Scheme 3). Under standard reaction conditions, there was no reaction between cyclopropane **3y** and amine **2a**; thus, the approach to product **4a** via a nucleophilic ring opening of cyclopropane **3y** was excluded (Scheme 3a). In order to trap the radical intermediate, we performed the reaction under oxygen. Lactone **5** was obtained in 37% yield while the malonylamination product **4a** was not observed (Scheme 3b), suggesting the involvement of a possible radical intermediate **int-5**. Then we further carried out a radical clock experiment (Scheme 3c). Under the standard reaction conditions, cyclopropane **3x** could react with arylamine **2d** and iodonium ylide **1a** to give the ring-opening product **4x**. Considering the possibility of further oxidation of intermediate **int-5** to a carbocation, a competitive reaction between *N*-ethylaniline **2a** (0.6 mmol, 2.0 equiv) and less nucleophilic diphenylamine **2b** (0.6 mmol, 2.0 equiv) was carried out (Scheme 3d). Consistent with the proposed reaction pathway, despite the presence of excess *N*-ethylaniline, product **4b** was predominantly formed (**4b**:**4a** > 20:1), as diphenylamine **2b** could generate a much more stable aminium radical cation intermediate albeit with weaker nucleophilicity in contrast to *N*-ethylaniline **2a**. This competitive experiment further indicates that a radical pathway is in operation in the C−N formation step rather than a nucleophilic trapping of a carbocation with the amine.

Scheme 3. Mechanistic Investigation



The proposed reaction pathway was depicted in Figure 2. Initially, the halogen-bonding complex between an iodonium ylide and amine would induce an electron-transfer process to generate an aminium radical cation and a malonyl radical anion. Subsequently, the in situ generated malonyl radical anion would abstract a proton from a proton shuttle (i.e., succinimide) to give the malonyl radical upon losing one molecule of iodobenzene. Then malonyl radical addition of double bonds would lead to the formation of carbon-centered radicals that then engage in the C−N bond formation with aminium radical cations. Finally, the anionic proton shuttle

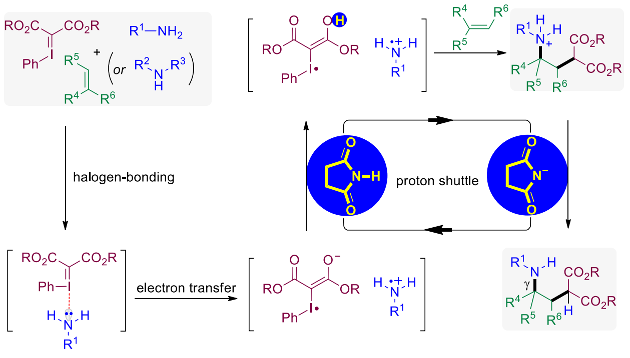


Figure 2. Proposed reaction pathway.

obtains a proton from the aminium cation to finish the bond-forming events.

In conclusion, we developed a malonylamination of alkenes using simple primary and secondary amines and iodonium ylides as starting materials. This transformation did not require any transition metals and external chemical oxidants, directly generating γ-amino acid derivatives. The presence of succinimide as a proton shuttle is essential for the high efficiency of this transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00983.

Full experimental procedures and compound characterization (PDF)

Accession Codes

CCDC 1881966 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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