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Visible-Light-Mediated Stereoselective 1,2-Iodoalkylation of Alkynes

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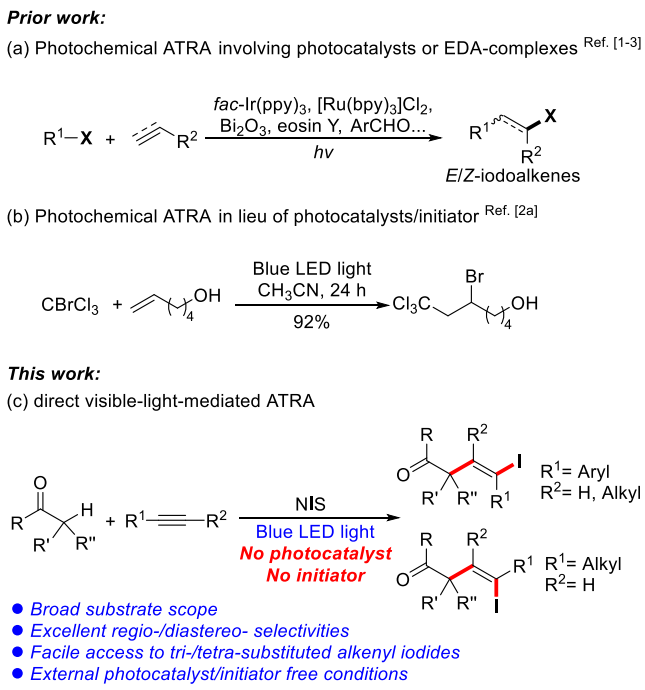
Abstract. A visible-light-mediated and photocatalyst/initiator-free addition to alkynes has been developed. An atom transfer radical addition (ATRA) mechanistic afforded a broad scope of valuable iodo-substituted alkenyl derivatives with high *E*/*Z*-selectivities, which are versatile intermediates for the synthesis of various tri- and tetra- substituted alkenes.

Keywords: visible-light-mediated; three component; stereoselective; iodo-substituted alkenes

The demand for synthetic strategies that proceed under mild and environmental benign conditions is one of the most pressing problems facing the synthetic community. Recent decades has witnessed the blooming of photochemical irradiation as a powerful approach for challenging transformations.[1] Typically, photocatalysts which are capable of engaging in the energy transfer (ET) or single-electron-transfer (SET) process are heavily employed in current photochemical reactions. On the other hand, there are relatively fewer examples of an organic transformation driven by visible-light without a photocatalyst.[2] Currently reported visible-light-induced organic reactions in the absence of photocatalysts deeply relied on the formation of electron-donor-acceptor (EDA) complex.[3] Thus, the development of effective photocatalyst-free transformations with substrates that were not capable of forming EDA complex is a challenging goal in organic synthesis but yet remains largely unexplored.

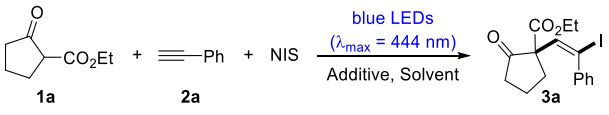
In the context of our continuous interest in the chemo- and stereo-selective functionalization of alkynes,[4] we envisioned that photochemical reactions induced by visible light could open up mild and general synthetic approaches to valuable substituted alkenyl derivatives. Atom transfer radical addition (ATRA) of haloalkanes to alkenes and alkynes serves as an atom-economical method of simultaneously forming C-C and C-X bonds, and it has been recognized as a useful tool in organic chemistry.[5] However, most ATRA required toxic and hazardous initiators, peroxides, organotins, and triethylboron, to name a few. By using light irradiation, the radical process could be initiated *via* a direct energy transfer,[5n-5p] otherwise, a photocatalyst was always required to activate the reactants which were not able to absorb the visible light (Scheme 1, Equation (a)).[1-3] Besides, these methods constantly employed harsh conditions and lack broad functional group tolerance. To the best of our knowledge, only a few examples induced by visible light in the absence of photocatalyst/initiator was reported to date (Scheme 1, Equation (b)).[2a] Nonetheless, the substrates were limited in multihalogen alkanes, while simple alkyl halides or their C-H precursors were not applicable. In this regard, we sought to develop a protocol capable of conducting ATRA with a broad scope under mild conditions without photocatalyst or radical initiator. Here we report a successful realization of a visible-light-mediated route to 1-iodoalkenyl products from readily available carbonyls and alkynes via ATRA pathway,[6] which proceeds under very mild conditions upon irradiation with blue light-emitting-diodes (LEDs). This process does not require the use of external photocatalyst or initiator and the generated products have proven to be flexible synthons in a variety of transformations.



Scheme 1. Photochemical ATRA approaches in the difunctionalization of alkynes.

Initially, the visible-light-mediated coupling of β-ketoester **1a**, phenylacetylene **2a** in the presence of NIS was designed (Table 1). To our delight, the desired product **3a** was generated in 11% yield after 3 hours at room temperature under the irradiation of blue LED light (λ_{max} = 444 nm) without any addition of external photosensitizer or initiator (entry 1). Optimization studies involving the screening of Lewis acids (entries 2-7), solvents (entries 8-11), halogenation reagents (entries 12-13) and light sources (entry 14) led to an significant improvement in the yield of **3a** to 83% isolated yield (*E*/*Z* 12/1) by using $Mg(ClO_4)_2$ as the additive and CH_3CN as the solvent (entry 7). On the contrary, a control experiment performed without irradiation by visible light was unproductive, indicating that the visible light irradiation was essential for this transformation (entry 15).

Table 1. Optimization of the reaction conditions[a]



Entry	Additive	Solvent	Temp. (°C)	Yield (%)	*E*/*Z*[b]
1	none	CH_3CN	40	11	9/1
2	$Cu(OTf)_2$	CH_3CN	40	38	10/1
3	$Fe(acac)_3$	CH_3CN	40	trace	nd[c]
4	$Sc(OTf)_3$	CH_3CN	40	74	11/1
5	$AgNO_3$	CH_3CN	40	trace	nd[c]
6	$Mg(ClO_4)_2$	CH_3CN	40	79	10/1
7[de]	$Mg(ClO_4)_2$	CH_3CN	35	83	12/1
8[ef]	$Mg(ClO_4)_2$	CH_3CN	35	71	12/1
9[de]	$Mg(ClO_4)_2$	Acetone	40	67	11/1
10[de]	$Mg(ClO_4)_2$	Toluene	40	66	7/1
11[de]	$Mg(ClO_4)_2$	CH_2Cl_2	40	70	8/1
12[g]	$Mg(ClO_4)_2$	CH_3CN	40	3	nd[c]
13[h]	$Mg(ClO_4)_2$	CH_3CN	40	1	nd[c]
14[i]	$Mg(ClO_4)_2$	CH_3CN	40	33	11/1
15[j]	$Mg(ClO_4)_2$	CH_3CN	40	3	nd[c]

[a] General conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), additive (30 mmol%), NIS (0.11 mmol, 25 mg) solvent (2 mL), blue LED light (λ_{max} = 444 nm) at argon for 3 hours. Isolated yields of the *E*/*Z*-isomers were given. [b] *E*/*Z* determined using ^1H NMR analysis. [c] nd: Not determined. [d] 10 mol% of $Mg(ClO_4)_2$ was used. [e] 2 equiv. of **2a** was used. [f] 5 mol% of $Mg(ClO_4)_2$ was used. [g] I_2 was used instead of NIS. [h] TMS-C≡C-I was used instead of NIS. Reaction time: 15 h. [i] Red LED light (λ_{max} = 620 nm) was used. [j] Reaction conducted under dark.

The scope of the reaction is shown in Schemes 2-5. A variety of different alkynes, including terminal aryl alkynes (Scheme 2), terminal alkyl alkynes (Scheme 3), internal alkynes (Scheme 4) and various dicarbonyls (Scheme 5) could be applied in this transformation and afford the corresponding iodo-substituted alkenes **3-6** in good to excellent yields (up to 92%). A range of diverse functional substituents including electron-withdrawing (F, Cl, Br, CO_2Me, CHO, CN, NO_2, CO_2H) and electron-donating groups (OMe, OH, Me, Bu-*t*) were well tolerated. In all cases, the products were obtained in excellent stereoselectivities. Interestingly, the *E*/*Z* selectivity could be easily regulated simply by switching the alkynes. *E*-iodoalkenes were generated as the major products for (hetero)aryl substituted alkynes (Schemes 2, 4-5) while *Z*-iodoalkenes were generated predominately with terminal alkyl alkynes (Scheme 3). The specific stereochemistry was also confirmed by an X-ray analysis of the coupling product **4g'**, generated from the **4g** (For preparation details and X-ray analysis of **4g'**, see SI for details). This three-component iodoalkylation was also compatible for a scaled-up experiment, in which the corresponding iodo-substituted styrene **3a** was furnished in 80% isolated yield with a perfect diastereoselecitivty (*E*/*Z* > 20/1) with only 1 mol% of the catalyst (Scheme S1, see SI for details).

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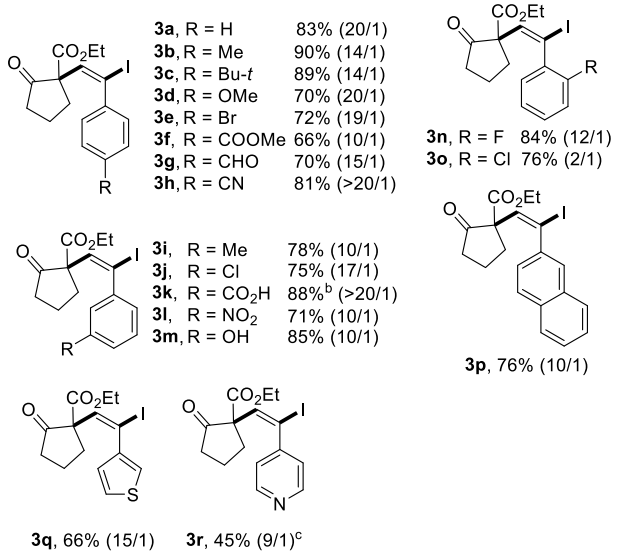
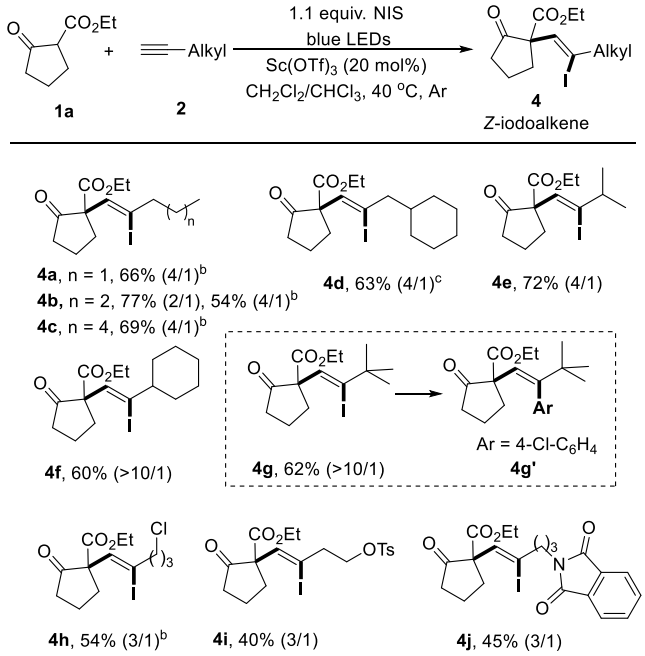


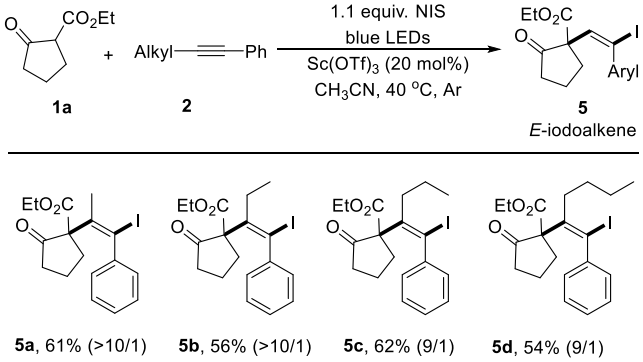
General Conditions: [a] **1a** (0.1 mmol, 15 µL), terminal aryl alkynes **2** (2 equiv), $Mg(ClO_4)_2$ (10 mol%, 2.3 mg), NIS (1.1 eq, 25 mg), CH_3CN (2 mL), blue LED light (λ_{max} = 444 nm) at argon for 3 h. Isolated yields of the *E*/*Z*-isomers were given. [b] NMR yield. [c] Reaction time: 12h.

Scheme 2. Substrate scope for aryl alkynes[a]



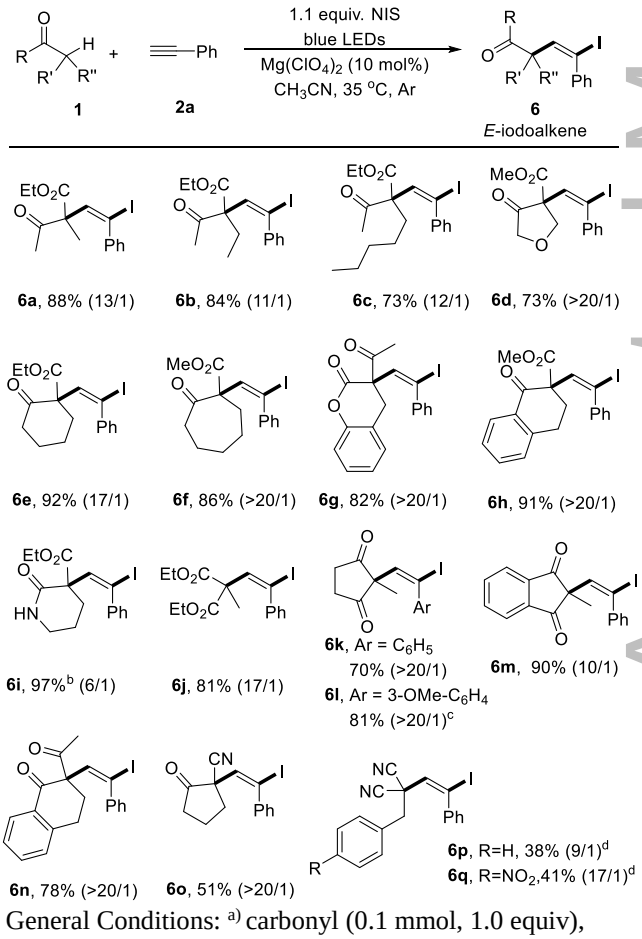
General conditions: [a] **1a** (0.1 mmol, 1.0 equiv, 15 µL), alkynes **2** (5 equiv), $Sc(OTf)_3$ (20 mmol%, 9.8 mg), NIS (1.1 eq, 25 mg), CH_2Cl_2 (2 mL), blue LED light (λ_{max} = 444 nm) at argon for 12 h. Isolated yields of the *E*/*Z*-isomers were given. [b] 10 mL of CH_2Cl_2 was used as solvent, 24 h. [c] 10 mL of $CHCl_3$ was used as solvent, 24 h.

Scheme 3. Substrate scope for terminal alkyl alkynes[a]



General conditions: [a] **1a** (0.1 mmol, 1.0 equiv, 15 µL), alkynes **2** (5 equiv), $Sc(OTf)_3$ (20 mmol%, 9.8 mg), NIS (1.1 eq, 25 mg), CH_3CN (2 mL), blue LED light (λ max = 444 nm) at argon for 24 h. Isolated yields of the E/Z-isomers were given.

Scheme 4. Substrate scope for internal alkynes[a]



General Conditions: [a] carbonyl (0.1 mmol, 1.0 equiv), alkyne **2a** (2 equiv, 22 µL), $Mg(ClO_4)_2$ (10 mol%, 2.3 mg), NIS (1.1 eq, 25 mg), CH_3CN (2 mL), blue LED light (λ_{max} = 444 nm) at argon for 3 h. Isolated yields of the E/*Z*-

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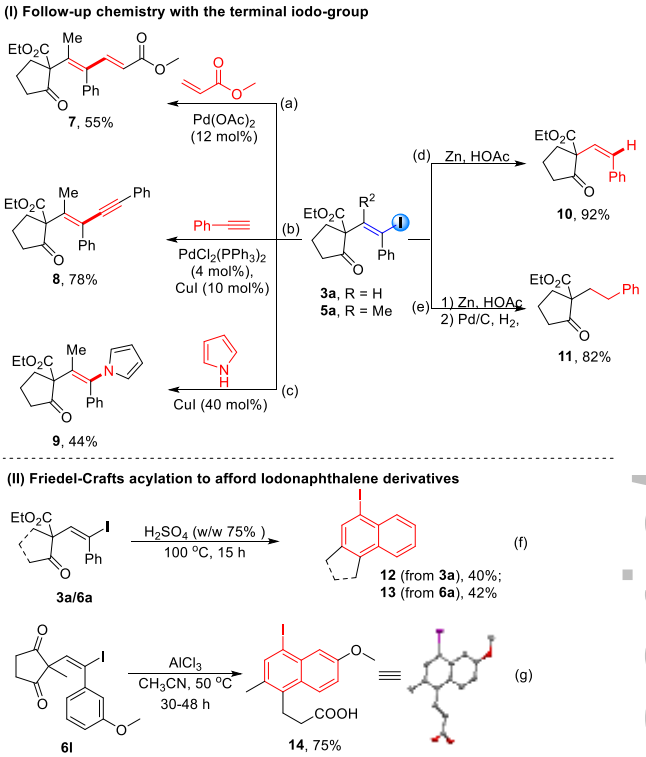
isomers were given. [b] NMR yield. [c] 5 mmol scale, 16 h. [d] Reaction time: 12h.

Scheme 5. Substrate scope for different dicarbonyls[a]

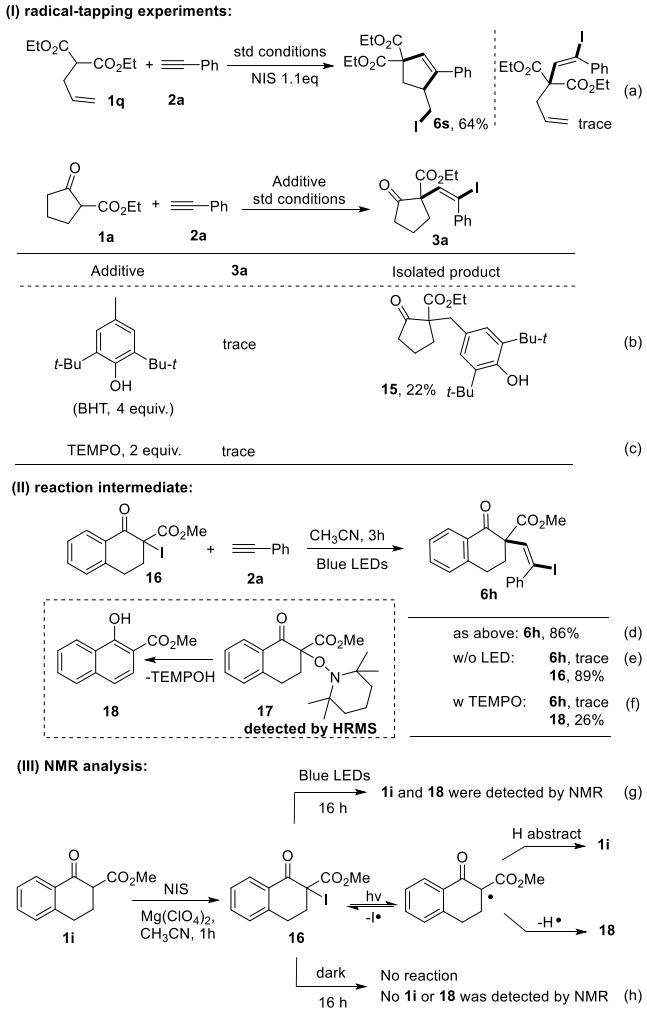
The application potential of the method was further explored by converting the terminal iodo-group by various reactions (Scheme 6). Thus, iodo-substituted alkene **5a** was subjected to Heck coupling (Equation (a)), Sonogashira reaction (Equations (b)) and CuI catalyzed C-N amination (Equation (c)) to give the conjugated unsaturated ester **7**, phenyl enyne **8** and *N*-vinyl pyrrole **9**, respectively. A selective deiodination of **3a** with Zn/HOAc afforded disubstituted alkene **10** (Equation (d)). The latter compound was further converted *via* Pd/C-catalyzed hydrogenation to afford phenethyl ketoester **11** (Equation (e)). Iodonaphthalene (NpI) and its derivatives are important building blocks in organic synthesis, pharmaceutical industry and material sciences.[7] The α-vinyl ketoester **3a** and **6a** easily underwent a Friedel-Crafts acylation to afford the fused 1-iodonaphthalene **12** and **13** smoothly (Equation (f)). Interestingly, when **6l** was subjected to a similar acylation, iodo-substituted naphthalenepropanoic acid **14** was isolated in good yields (Equation (g)). An arenium cation was proposed to be involved in this fragmentation in the presence of $AlCl_3$ (see SI, Scheme S2).[8] Multi-substituted naphthalenepropanoic acid consist an important structural motif in marine natural products and pharmaceutical candidates.[9] This straightforward synthesis of iodo-substituted naphthalenepropanoic acid will certainly benefit the chemistry community.



Scheme 6. Various transformations pertaining to the iodo-substituted alkenes.

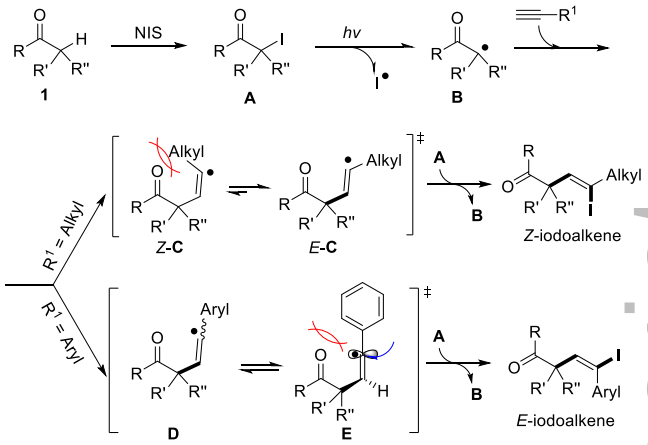
Several control experiments for the elucidation of mechanism was summarized in Scheme 7. When the reaction of 2-allyl malonate **1q** with alkyne **2a** was performed under the standard reaction conditions, the expected 1,2-iodoalkylation product was not observed (equation (a)). Instead an iodomethyl substituted cyclopentene **6s** was isolated in 64 % yield, which strongly consisted with a radical pathway. In the presence of a radical scavenger (Butylated hydroxytoluene (BHT) or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO)) (Equations (b-c)), only trace of the desired products **3a** was formed, while the adduct **15** was isolated, indicating an involvement of ketoester radical intermediate (see SI for details). Furthermore, we have successfully isolated α-iodo intermediate **16** in the absence of alkyne. As expected, irradiation of the α-iodo intermediate **16** with additional alkyne **2a** did afford the desired product **6h** in a comparable yield (86%). A complete shutdown of reactivity was observed without visible light or in the presence of TEMPO, thus suggesting that **16** might be a possible intermediate (equations (d-f)). We speculated that the C-I bond dissociation might be the crucial step, thus we prepared its bromo analogue **16-Br**, and subjected it to the standard reaction conditions. As expected, no reaction occurred, probably due to the high dissociation energy required for the C-Br bond (see SI for details). On the other hand, 1-hydroxy-2-naphthoate **18**, formed by decomposition of **17**, was also isolated (see SI for details). The ^1H NMR analysis of the crude mixture of the *in situ* generated

16 under blue LED irradiation or dark condition further supported that the direct photolysis of the **16** was the first step to induce the radical process (equations (g-h) and Figure S3). And the UV-visible absorption of the **1i**, **2a**, **16** and **6h** were also conducted to prove this process (Figure S5).



Scheme 7. Investigation of the Mechanism.

Based on previous investigations[10] and our present data, the following reaction mechanism is proposed (Scheme 8). The reaction was initiated by visible light irradiation/Lewis acid catalysis, generating α-carbonyl radical **B** with the release of iodide radical. An intermolecular addition of the α-carbonyl radical **B** with alkynes afforded the γ-carbonyl vinyl radicals **C** (R^1 = Alkyl) and **D** (R^1 = Aryl), respectively. The preferred *Z*-selectivity for alkyl alkynes likely depended on the relative stability of the *E*/*Z*-intermediates, with *E*-**C** being more stable to give the *Z*-iodo alkenes as the major products. When (hetero)aryl alkynes were used, the generated radicals **D** would likely isomerize to a more stable π-radical **E**,[11] which subsequently reacted with α-iodo dicarbonyl intermediate **A** to deliver the final products while releasing the radical **B** to regenerate the radical process (a quantum yield of 11.6 was measured and again supported this chain reaction pathway, see SI for details). The excellent *E*-configuration control may be ascribed to steric hindrance that **A** would like to approach the radical from less steric direction (for related examples and study, see ref 11).



Scheme 8. Hypothetical cascade radical pathway.

In summary, we have developed a novel visible-light-mediated intermolecular ATRA coupling of carbonyls, alkynes and NIS under mild conditions without external photocatalyst or radical initiator. The generated functionally diverse iodo-substituted alkenyl derivatives may be of interest in pharmaceutical or material sciences as they have proven to be valuable building blocks in a variety of transformations, some of which were demonstrated in this work. Further applications of this mild ATRA transformation is currently on-going in our lab and will be reported in due courses.

Experimental Section

Representative procedure for the three component coupling:

For terminal aryl alkynes: $Mg(ClO_4)_2$ (0.01 mmol, 2.3 mg), NIS (0.11 mmol, 25 mg) and aromatic alkynes **2** (0.2 mmol, if solid) were placed in an oven-dried Schlenk-tube. The tube was evacuated and filled with argon for four times. A solution of β-Ketocarbonyl **1** (0.1 mmol) and aromatic alkynes **2** (0.2 mmol, if liquid) in CH_3CN (2 mL) was added at RT. The reaction mixture was irradiated under 9.6 W blue LEDs (λ_{max} = 444 nm) at RT and stirred for 3 hours. The resulting mixture was directly subjected to flash column chromatography on silica gel to afford the desired products **3**, **6**.

For the procedure of internal and aliphatic alkynes, detailed experimental procedures, characterization data, mechanism study, copies of ^1H and ^{13}C NMR spectra, see SI.

CCDC 1845340 (**3a**), 1845341 (**6h**), 1845342 (**5a**), 1845343 (**4g'**) and 1845344 (**14**) contain the

supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Acknowledgements

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