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Catalyst-Free C*sp*–C*sp*^{3} Cross-Coupling of Bromodifluoroacetamides with 1-Iodoalkynes under Visible-Light Irradiation

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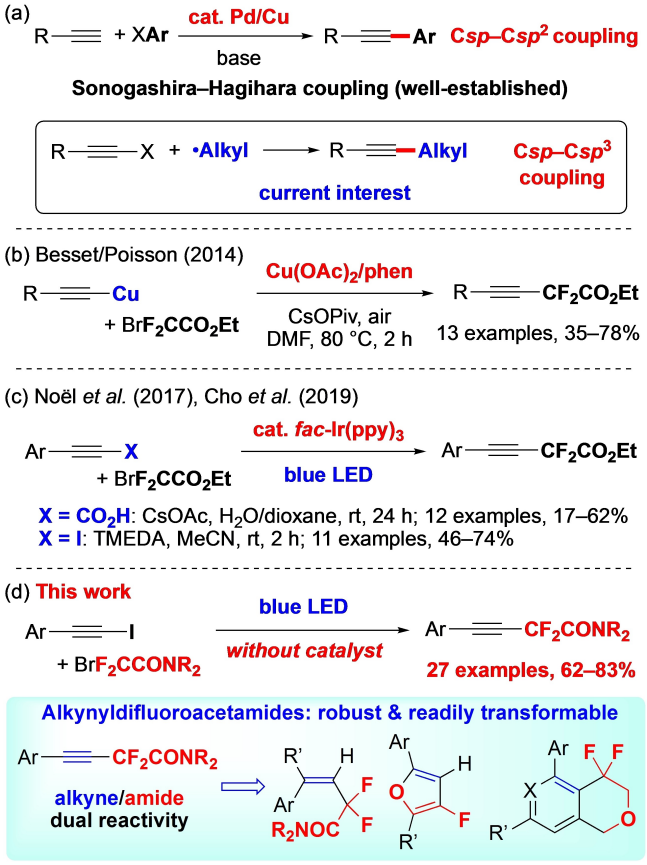
Abstract: We describe herein that the cross-coupling of bromodifluoroacetamides with (iodoethynyl)arenes proceeds without recourse to any photocatalyst when exposed to visible light at room temperature to afford alkynyldifluoroacetamides in 62–83% yields (27 examples). Several control experiments suggest that the reaction involves the homolysis of bromodifluoroacetamides and the coupling of the resultant difluoromethyl radical species with the 1-iodoalkynes via a radical chain process. Divergent transformations of the coupling products led to various organofluorine compounds, demonstrating the synthetic utility of the developed photocoupling method.

Keywords: Alkyne; Cross-coupling; Difluoroalkylation; Photoreaction; Radical

Introduction

Alkynes are highly useful starting materials in organic synthesis. Diverse methods to introduce alkynyl substituents via transition-metal-catalyzed C*sp*–C*sp*^{2} cross-couplings (Sonogashira–Hagihara and related reactions) for the synthesis of arylalkynes and 1,3-enynes have been extensively developed (Scheme 1a).[1] On the other hand, aliphatic alkynes have been conventionally prepared via the alkylation of metal acetylides. However, this method is not compatible with reactive functional groups because of the high nucleophilicity of acetylides. Therefore, radical alkynylations have recently been investigated as an alternative method with a wide functional group tolerance.[2]

The introduction of fluorine atoms into drug molecules can enhance their biological activity by modifying various molecular properties, such as lipophilicity, metabolic stability, conformational rigidity, and binding affinity to target proteins.[3] Therefore, an efficient and divergent method for the synthesis of organofluorine compounds has been sought after. One viable approach is the building block method, in which reactive fluorinated small molecules are used as versatile molecular scaffolds to assemble complex fluorinated molecular architectures.[4] In this respect, fluoroalkyl-substituted alkynes are particularly intriguing as their carbon-carbon triple bonds undergo a diverse array of organic transformations.[5] Although the synthesis of fluoroalkyl-substituted alkynes has been investigated extensively, the reported methods are largely limited to the introduction of saturated fluoroalkyl groups using stoichiometric copper salts and/or expensive fluoroalkylating reagents.[6] Thus, the development of a new method to introduce difluoromethyl carbonyl groups without recourse to stoichiometric copper salts (Scheme 1b) and expensive reagents is desired.[7] To meet these requirements, several methods to synthesize alkynes bearing a difluoroacetate moiety by taking advantage of visible light photoredox catalysis have been recently developed (Scheme 1c).[8] Noël and coworkers re-



Scheme 1. Previous examples of the synthesis of alkynyldifluoroacetates under photocatalytic conditions and catalyst-free synthesis of alkynyldifluoroacetamides.

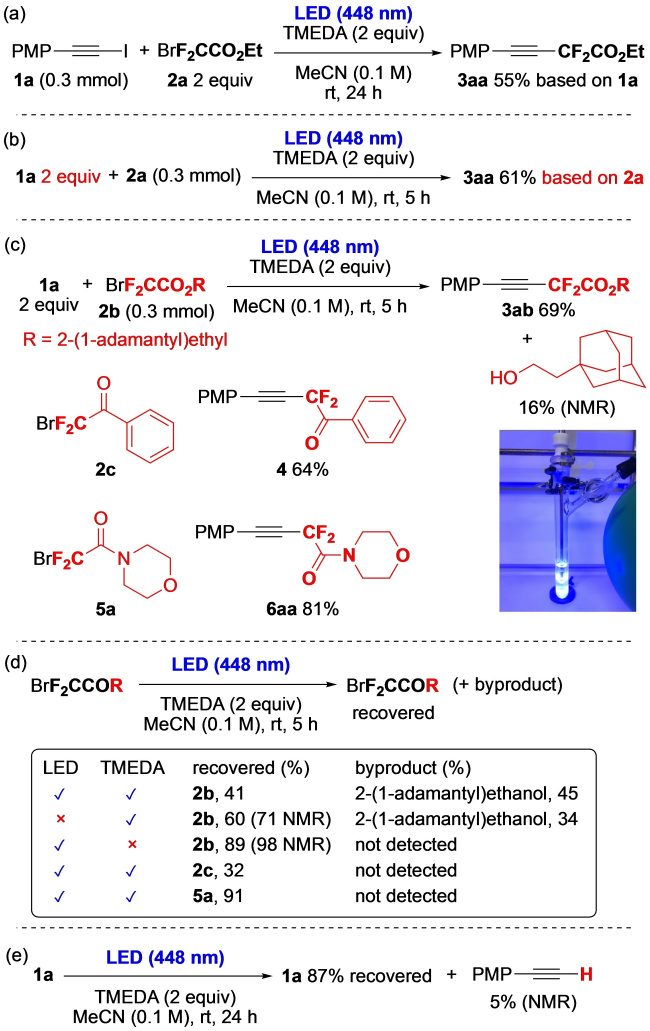
ported the decarboxylative cross-coupling reaction of 3-arylpropiolic acids with ethyl bromodifluoroacetate under photocatalytic conditions, producing alkynyl-substituted difluoroacetates in 17–62% yields.[8a] Later, Cho and coworkers developed the coupling of 1-iodoalkynes with ethyl bromodifluoroacetate under different photocatalytic conditions.[8b] In the latter study, heteroaryl-substituted alkynes were compatible, and the product yields were somewhat improved (46–74%). In addition, Ko and coworkers reported the photocatalytic coupling of terminal arylalkynes with perfluoroalkyl iodides, albeit requiring a long reaction time (40 h).[8c] Although these methods are advantageous, as difluoroalkylation proceeds under mild reaction conditions, an expensive iridium-based photoredox catalyst is required and the product yield is less than 74%. Moreover, the synthetic potential of the coupling products was not demonstrated in these reports.

Our group have been involved in the development of the Cu-catalyzed hydroarylation of electron-deficient alkynes and its application to the synthesis of biologically active compounds.[9] We recently reported the Cu-catalyzed hydroarylation of (trifluoromethyl) alkynes and a mechanistic study of this reaction using density functional theory (DFT) calculations.[10] As a part of our research project, we became interested in the synthesis of alkynes bearing a functionalized difluoroalkyl group and their transformations via Cu-catalyzed hydrofunctionalization. However, two challenges must be overcome. First, the previously reported methods (Scheme 1c) require a precious metal photocatalyst and the product yields and scalability should be improved. Second, alkynyldifluoroacetates readily undergo ester exchange under Cu-catalyzed hydroarylation conditions (in methanol at 28 °C) to afford a mixture of inseparable products. Therefore, we developed a new catalyst-free photo-induced cross-coupling reaction of bromodifluoroacetamides with 1-iodoalkynes (Scheme 1d). Herein, we present the results of this study and the divergent transformations of the coupling products obtained.

Results and Discussion

Initial assessment of bromodifluoromethyl carbonyl compounds. We revisited the Cho's cross-electrophile coupling of 1-iodoalkynes with ethyl bromodifluoroacetate to develop metal-free conditions using an organophotocatalyst instead of an Ir photocatalyst. A solution of *p*-methoxyphenyl (PMP)-substituted iodoalkyne **1a** (0.3 mmol), ethyl bromodifluoroacetate (**2a**, 2 equiv), and *N*,*N*,*N*',*N*'-tetramethylenediamine (TMEDA) (2 equiv) in dry degassed acetonitrile was irradiated using a LED lamp equipped inside the reaction tube (Scheme 2). Unexpectedly, we found that the reaction proceeded without any photocatalyst under irradiation (blue LED, 448 nm) for 24 h to afford the desired product **3aa** in a modest yield, along with several byproducts having two ester groups (Scheme 2a). However, we failed to improve the yield although various reaction parameters were examined (Table S1 in the Supporting Information).

We further investigated this catalyst-free reaction in detail. At the outset, we checked the product yields and conversion of 1-iodoalkyne **1a** during the reaction to gain insights into the reaction progress (Figure S1 in Supporting Information). The yield of **3aa** gradually increased and reached a maximum (57%) in approximately 6 h. However, the yield did not increase after this period and slightly decreased (55%) after 24 h with an increase in the proportion of byproducts. Notably, the difference between the yield of **3aa** and the conversion of **1a** gradually increased during the reaction period. These reaction profiles suggest that the 1:1 coupling of **1a** with **2a** stops at approximately 6 h and that **3aa** reacts with **2a** to form byproducts throughout the reaction time. Therefore, we decided to use **2a** as the limiting agent and an excess of **1a** to suppress the formation

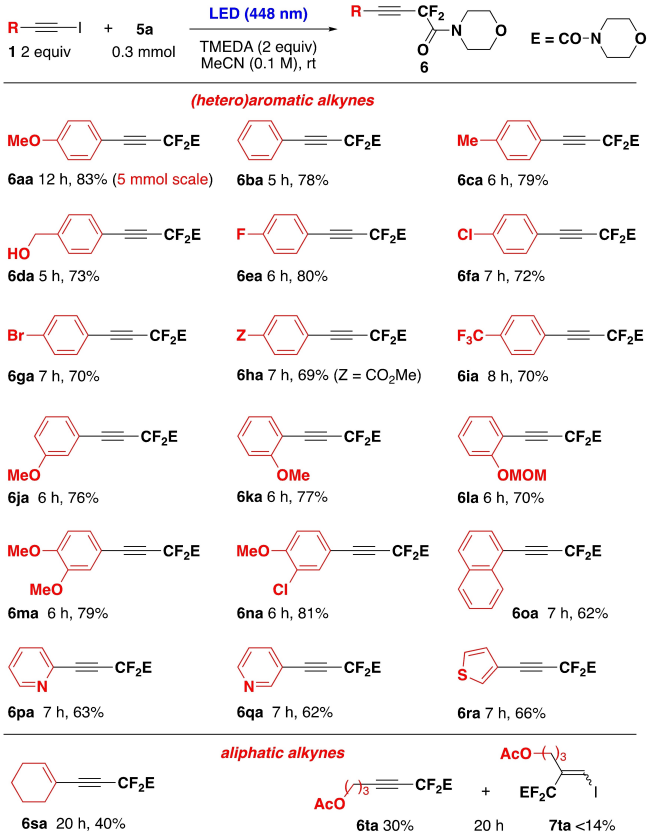


Scheme 2. Coupling of 1-iodoalkyne **1a** with bromodifluorocarbonyl compounds and robustness tests of bromodifluorocarbonyl compounds **2** and 1-iodoalkyne **1a** (PMP = *p*-methoxyphenyl).

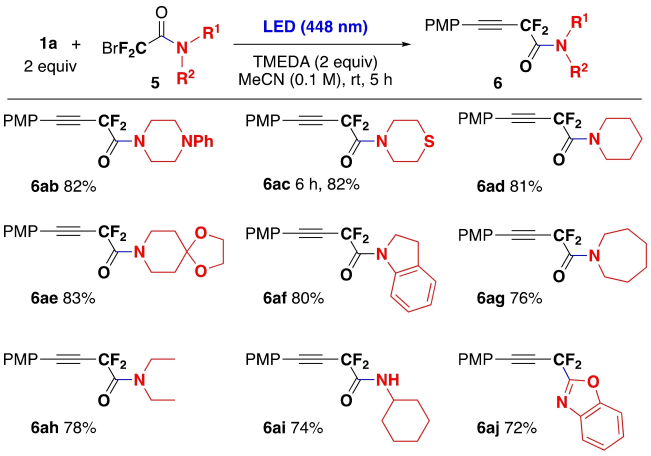
of byproducts. Thus, **2a** (0.3 mmol) was allowed to react with **1a** (2 equiv) under irradiation (blue LED) for 5 h to afford **3aa** in a slightly improved 61% yield (Scheme 2b). Although **2a** was fully consumed after the reaction, no byproduct was detected in the crude product by ^{19}F and ^{1}H NMR spectroscopy, suggesting that **2a** decomposed during the reaction. To identify the decomposition products, the coupling reaction was repeated using 2-(1-adamantyl)ethyl ester **2b** instead of **2a** (Scheme 2c). Accordingly, 2-(1-adamantyl)ethanol was detected in the crude product mixture, and the corresponding coupling product **3ab** was isolated in 69% yield. Because the decomposition of bromodifluoroacetates under reaction conditions was suggested, the reactivity of bromodifluoromethyl phenyl ketone (**2c**) and bromodifluoroacetamide **5a** toward 1-iodoalkyne **1a** was investigated. When ketone **2c** was used, the corresponding coupling product **4** was obtained in a comparable yield (64%) with that of **3ab**. No side products were detected in the crude reaction mixture. In contrast, the reaction using amide **5a** afforded **6aa** in a much higher yield (81%).

These results imply that the stability of the above bromodifluoromethyl carbonyl compounds under photo-coupling conditions depends on the electrophilicity of the carbonyl groups. In fact, ester **2b** and ketone **2c** were subjected to the reaction conditions in the absence of **1a** to obtain unreacted compounds in 41% and 32% recovery yields, respectively (Scheme 2d). Notably, the decomposition of **2b** was observed without irradiation; **2b** was recovered in 60% yield, and 2-(1-adamantyl)ethanol was obtained in 34% yield. In contrast, upon irradiation in the absence of TMEDA, most **2b** was recovered, and 2-(1-adamantyl)ethanol was not detected. Accordingly, the decomposition is likely induced by TMEDA and is enhanced by photoirradiation, although the details are unclear at this stage. Less electrophilic amide **5a** was recovered in 91% yield after irradiation in the presence of TMEDA, showing the robustness of **5a** under photo-coupling conditions. Therefore, bromodifluoroacetamides were identified as the optimal coupling partners for photo-coupling with 1-iodoalkynes. The tolerability of 1-iodoalkyne **1a** under irradiation conditions was also tested (Scheme 2e). When **1a** was subjected to photo-coupling conditions in the absence of a coupling partner for 24 h, 87% of **1a** was recovered. Only small amounts of the de-iodinated byproduct were detected in the crude product mixture.

Scope and limitations of photo-coupling of bromodifluoroacetamides with 1-iodoalkynes. The scope of the photo-coupling of bromodifluoroacetamide **5a** with 1-iodoalkynes was investigated, as outlined in Scheme 3. Phenyl-, *p*-tolyl-, *p*-(hydroxymethyl)phenyl-, and *p*-fluorophenyl-substituted 1-iodoalkynes **1b–e** gave the corresponding coupling products **6ba–ea** in good yields. Notably, the benzylic alcohol moiety of **1d** was well tolerated. The reaction of iodoalkynes **1f** and **1g**, bearing a *p*-chlorophenyl or *p*-bromophenyl substituent, also delivered **6fa** and **6ga** in good yields, although prolonged reaction times were required. 1-Iodoalkynes **1h** and **1i** bearing an electron-withdrawing group such as CO_2Me and CF_3 on the aryl terminal, furnished the corresponding coupling products **6ha** and **6ia** in 69% and 70% yields, respectively. In addition to *p*-substituted aryl groups, *m*- or *o*-substituted aryl groups were also compatible with this method, as coupling products **6ja–na** were obtained in 70–81% yields. 1-Naphthyl derivative **6oa** was also obtained in 62% yield. As heteroaryl derivatives, iodoalkynes **1p–r**, bearing a 2-pyridyl, 3-pyridyl, or 3-thiophenyl group, underwent the



Scheme 3. Scope of 1-iodoalkyne substrates.



Scheme 4. Scope of bromodifluoroacetamides (PMP = *p*-methoxyphenyl).

photo-coupling to give **6pa–ra** in 62–66% yields. The present catalyst-free photo-coupling reaction is scalable: the reaction of **1a** and **5a** was performed in a 5 mmol scale for 12 h to afford **6aa** (1.38 g) in 83% yield.

In contrast to (hetero)aryl-substituted 1-iodoalkynes, aliphatic 1-iodoalkynes exhibited lower reactivity. The reaction of cyclohexenyl-substituted 1-iodoalkyne **1s** required a much longer reaction time (20 h), and the desired product **6sa** was obtained in a moderate yield (40%). The reaction of alkyl-substituted 1-iodoalkyne **1t** with **5a** gave the expected product **6ta** in 30% yield along with byproduct **7ta** in a low yield. This result suggests that the unsaturated terminal group of 1-iodoalkynes is necessary for the regioselective radical addition.

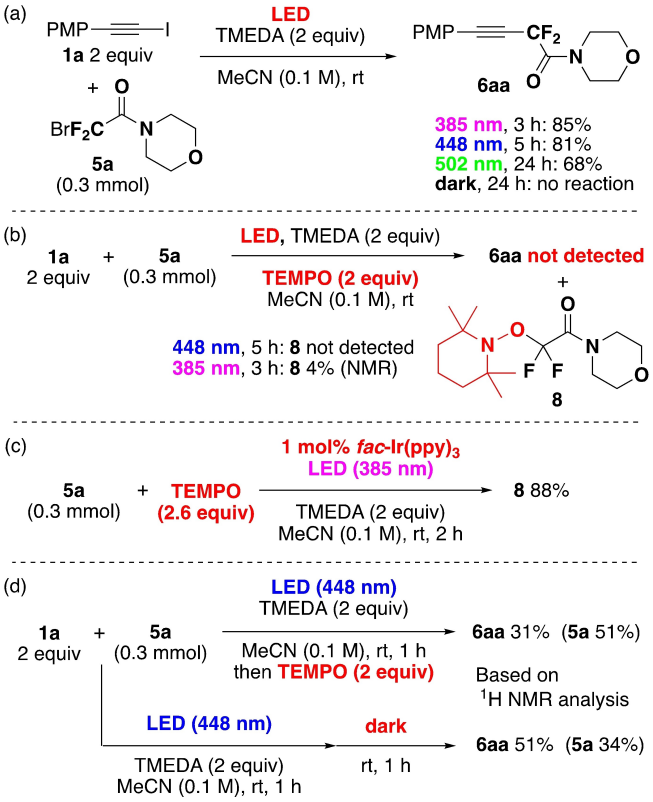
The scope of bromodifluoroacetamides was also investigated, and the results are summarized in Scheme 4. *N*-Phenylpiperadine and thiomorpholine moieties in amides **5b** and **5c** were well tolerated under the reaction conditions to furnish the desired products **6ab** and **6ac** in 82% yield. Similarly, amides with a five- to seven-membered carbocyclic amine moiety (**5d–g**) gave the corresponding products **6ad–ag** in 76–83% yields. The use of *N*,*N*-diethylacetamide **5h** afforded **6ah** in a good yield, indicating that the cyclic amine moiety was unnecessary. Secondary amide **5i** also participated in the coupling reaction, affording **6ai** in a good yield. In addition to these amides, 2-bromodifluoromethyl-1,3-benzoxazole (**5j**) successfully reacted with **1a** to produce **6aj** in 72% yield.

Mechanistic considerations. To obtain insights into the mechanism of the catalyst-free photo-coupling, several control experiments were conducted as follows. UV/Vis spectroscopic measurements of the reaction components were carried out (Figures S2–S5 in Supporting Information). The UV/Vis spectral charts of a mixture of TMEDA and bromodifluoroacetamide **5a** or a mixture of TMEDA and 1-idoalkyne **1a** in acetonitrile were almost identical to that of a solution of TMEDA alone (Figures S3 and S4). No coloration was observed when **1a** and **5a** were mixed with TMEDA in acetonitrile (Figure S5 in Supporting Information). Moreover, the UV/Vis spectral charts of solutions of **5a** and TMEDA with different ratios (**5a**: TMEDA = 1:2 and 1:6) were similar with that of the 1:1 solution (Figure S6). These facts suggest that the formation of an electron-donor-acceptor (EDA) complex from **5a** and TMEDA is less possible. This was also corroborated by DFT calculations. Model EDA complexes between trimethylamine and α-halocarbonyl compounds were optimized at the ωB97X–D [SMD (MeCN)]6-311 + G(d,p)–SDD(d) level of theory (Table S2 in Supporting Information). The calculation of the EDA complex of $Br_3CCONMe_2$ (**s1**) gave an N(amine)–Br distance (2.715 Å), which is similar to that reported for the EDA complex between Br_3CCONH_2 and tetramethyl-*p*-phenylenediamine (2.722 Å).[11] The interaction energy (ΔE) value estimated for the former (−3.36 kcal/mol) is also similar to that reported for the latter (−4.53 kcal/mol).[11] A model EDA complex of $BrCF_2CONMe_2$ (**s2**), which is relevant to this study, was compared to those of

$BrCF_2CO_2Me$ and ICF_2CO_2Me (**s3** and **s4**, respectively) because the latter types of esters were employed in the photoreactions involving EDA complexes.[12] Although the N(amine)–X distance in **s2** (2.824 Å) is shorter than the sum of the van der Waals radii of the Br and N atoms (3.40 Å),[13] it is significantly longer than those of **s3** (2.794 Å) and **s4** (2.765 Å), implying that **s2** is much less stable than **s3** and **s4**. Instability is also indicated by the calculated interaction energies (−1.85 kcal/mol for **s2** vs. −3.70 and −5.79 kcal/mol for **s3** and **s4**, respectively). Natural bond orbitals (NBO) analyses also showed that the donor-acceptor interaction energy of **s2** was the smallest among the calculated models. Therefore, the formation of EDA complexes from bromodifluoroacetamides with TMEDA is less favored than those of bromodifluoroacetates and iododifluoroacetates.

Because the reaction mixture turned pale yellow after reaction completion, we checked the UV/Vis spectra of the supernatant solution and a solution of **6aa** in MeCN; however, no significant absorption was observed in the visible spectral region (Figures S8 and S9 in Supporting Information). Previously, Postigo *et al.* proposed that TMEDA/I_2 complex acts as a radical initiator.[14] However, the reaction of **1a** and **5a** in the presence of I_2 (30 mol%) under irradiation with a blue LED was incomplete within 5 h; **6aa** was obtained in 75% yield and 10% of **5a** was remained intact. Therefore, the initiation by TMEDA/I_2 is unlikely. Accordingly, the initiation mechanism is unclear, although the generation of an EDA complex **5**•TMEDA in a very low concentration cannot be completely excluded. The photo-coupling of **1a** with **5a** was repeated upon irradiation using LEDs of different wavelengths (Scheme 5a). Upon irradiation using a purple LED (385 nm), **6aa** was obtained in a slightly higher yield than that for the reaction using a blue LED, albeit with a shorter irradiation time. On the other hand, when a green LED (502 nm) was used, the reaction was very sluggish. The yield of **6aa** decreased to 68%, even after irradiation for 24 h. No reaction occurred in the dark.

Subsequently, the coupling of **1a** with **5a** was performed using a blue LED in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (2 equiv) as the radical-trapping agent for 5 h (Scheme 5b). As a result, the coupling product **6aa** was not detected in the crude reaction mixture by ^1H and ^{19}F NMR analyses. The coupling reaction in the presence of TEMPO was repeated with irradiation using a purple LED for 3 h. The TEMPO adduct (**8**) could be detected, albeit in only 4% yield, as estimated by ^1H NMR analysis of the crude mixture. These results imply that the radical species are involved in the photo-coupling reaction. Moreover, **5a** and TEMPO (2.6 equiv) was irradiated using a purple LED



Scheme 5. Control experiments (PMP = *p*-methoxyphenyl).

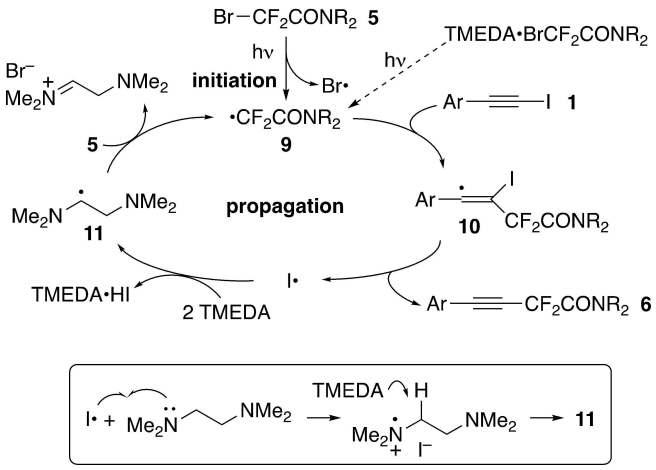
(385 nm) in the presence of the photocatalyst [*fac*-$Ir(ppy)_3$] for 2 h, affording TEMPO adduct **8** in 88% yield (Scheme 5c). On the other hand, **1a** and TEMPO (2 equiv) were also irradiated (385 nm) for 24 h. However, the TEMPO-alkyne adduct was not detected. These control experiments suggest that the homolytic cleavage of the C–Br bond of **5a** is facilitated under photo-irradiation to produce a difluoromethylacetamide radical species. However, its concentration is much lower than that under photoredox catalytic conditions.

The photo-coupling of **1a** and **5a** was performed under irradiation with a blue LED for 1 h, and the reaction was quenched by adding TEMPO (2 equiv), affording **6aa** in 31% yield based on ^1H NMR analysis of the crude reaction mixture (Scheme 5d). In contrast, the yield of **6aa** increased up to 51% when the reaction mixture was irradiated for 1 h, and then was stirred for another 1 h in the dark. These results suggest that the coupling reaction could continue after photoirradiation is stopped. However, continuous irradiation is required to ensure complete conversion of amide **5a**, due to termination pathway(s); **6aa** was obtained in 24% and 59% of **5a** was recovered when the reaction was performed with irradiation for 10 min and then the reaction mixture was stirred for 5 h in the dark.

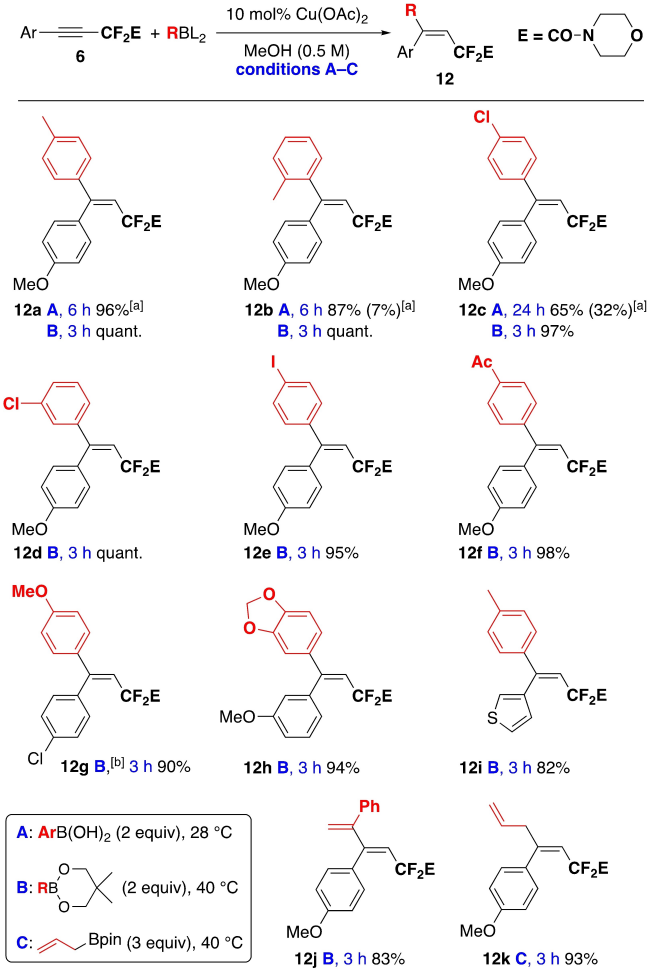
Scheme 6 shows a plausible mechanism based on the control experiments above. Under catalyst-free conditions, the coupling of bromodifluroacetamides **5** with iodoalkynes **1** proceeds via a radical chain mechanism. The initiation step is the photo-induced homolytic cleavage of the C–Br bond in **5**, generating a difluoroalkyl radical species **9**. The addition of **9** to 1-iodoalkyne **1** generates vinyl radical **10**. This step proceeds regioselectively because of the stabilization of vinyl radical with the conjugated aryl group. Subsequent elimination of the iodine atom (I·) produces coupling product **6**. The generated iodine atom undergoes single-electron reduction by TMEDA to generate radical species **11**, as depicted in the inset scheme. Finally, single-electron transfer from **11** to bromodifluroacetamides **5** regenerates difluoroalkyl radical **9**, closing the propagation cycle. It is noteworthy that the iodoalkynes play a significant role as radical acceptors. The reaction of 1-bromoalkyne **1a-Br** with bromodifluoroacetamide **5a** under the standard conditions afforded coupling product **6aa** in 78% yield, although a longer reaction time (7 h) was required (Scheme S1a, in Supporting Information). In striking contrast, coupling product **6ba** was not obtained from 3-phenylpropiolic acid. Moreover, the reaction of indole-2-carboxylate **s5** with bromodifluoroacetamide **5a** did not proceed under the catalyst-free conditions, while the expected coupling product **s6** was obtained in 55% yield under the photoredox catalytic conditions reported by Cho *et al.* (Scheme S1, in Supporting Information).[15] These results imply that the chain propagation step mediated by iodine atom and TMEDA is more decisive than the initiation step in the present catalyst-free photo-coupling.

Divergent transformation of the coupling products. Because alkynes equipped with a difluoroacetamide group are potentially useful building blocks, we investigated the transformations of the coupling products obtained in this study. At the outset, Cu-catalyzed hydroarylation with arylboron reagents was applied to coupling products **6** (Scheme 7). The reaction of alkynyldifluoroacetamide **6aa** with *p*- and *o*-tolylboronic acids was performed in the presence of 10 mol% $Cu(OAc)_2$ in methanol at 28 °C for 6 h. The corresponding hydroarylation products **12a** and **12b** were obtained in 96% and 87% yields, respectively, based on ^{1}H NMR analysis of the crude products. In contrast, the reaction of **6aa** with *p*-chlorophenylboronic acid was sluggish at room temperature, and undesired protodeboration occurred at elevated temperatures.

DFT calculations of the model reactions revealed that the activation barrier calculated for the rate-determining carbocupration of (2-phenylethynyl) difluoroacetate (18.4 kcal/mol) was slightly lower than that for phenyl(trifluoromethyl)acetylene (19.7 kcal/mol),[10c] as shown in Figure S10 (Supporting Information). In contrast, the corresponding activation barrier



Scheme 6. Plausible reaction mechanism.



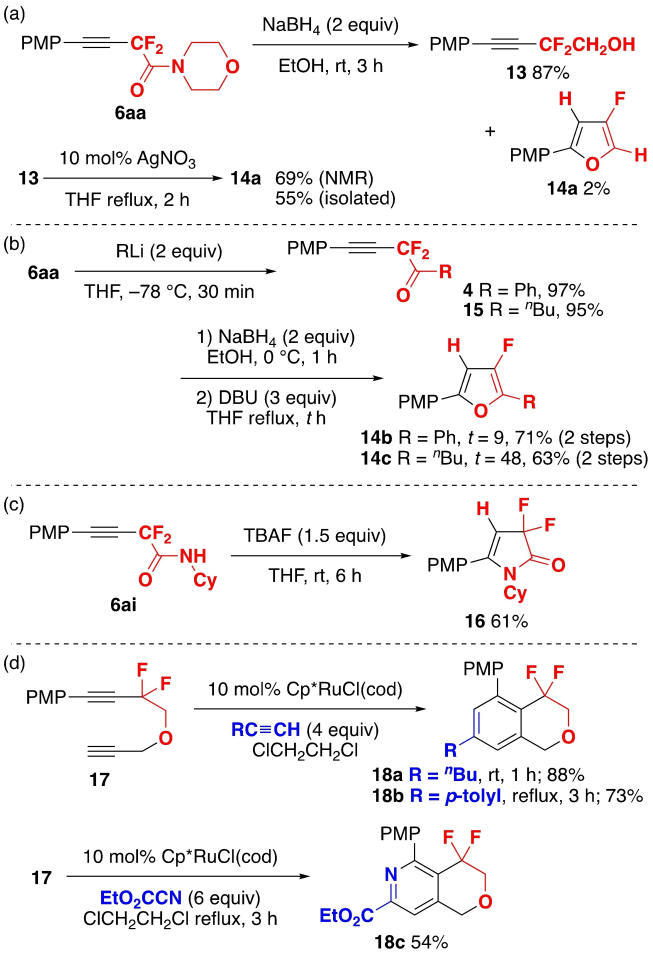
Scheme 7. Hydrofunctionalization of coupling products. [a] Yields were determined by ^{1}H NMR analysis of the crude products. Yields of recovered starting materials are shown in parentheses. [b] $Cu(OAc)_2$ (15 mol%) were used.

estimated for (2-phenylethynyl)difluoroacetamide (24.6 kcal/mol) is approximately 5 kcal/mol higher than those of (2-phenylethynyl)difluoroacetate and phenyl(trifluoromethyl)acetylene. Thus, the hydroarylation of alkynyldifluoroaetamides requires harsher reaction conditions. Therefore, *p*-chlorophenylboronic acid neopentyl glycol ester was used to avoid protodeborylation at an elevated temperature. The reaction of **6aa** with *p*-chlorophenylboronate was conducted at 40 °C for 3 h to obtain the desired product **12c** in 97% yield. Similarly, **12a** and **12b** were quantitatively obtained using the corresponding arylboronates at 40 °C. The reactions using other arylboronates also furnished hydroarylation products **12d–h** in high yields, although 15 mol% $Cu(OAc)_2$ was necessary for the formation of **12g**. It is worth noting that constitutional and stereoisomers (e.g., **12c**, **12d**, and **12g**) could be precisely synthesized using this method. The 2-thienyl ring of the alkyne substrate was also tolerated, as **12i** was obtained, albeit with a slightly diminished yield (82%). Similarly, hydrovinylation product **12j** was successfully obtained in 83% yield. Moreover, the reaction of **6aa** with allylboronic acid pinacol ester efficiently furnished skipped diene **12k** in 93% yield.

N-Difluoroacetylmorpholines are versatile difluoroalkyl building blocks because their amide moieties can be readily transformed into various functional groups.[16] Thus, we investigated the selective carbonyl transformations of the alkynyldifluoroacetamide product with its alkyne moiety preserved. The reduction of **6aa** was carried out using $NaBH_4$ (2 equiv) in ethanol at room temperature for 3 h to afford the desired alcohol **13** in 87% yield along with trace amounts of 3-fluorofuran **14a** (Scheme 8a). Furan **14a** should be produced via cyclization of **13** under basic conditions, since base-promoted cyclization of similar 2-alkynyl-2,2-difluoro alcohols has been reported.[17] Furan **14a** was obtained in a moderate yield when alcohol **13** was heated in THF in the presence of 10 mol% $AgNO_3$.[18]

The treatment of **6aa** with organolithium reagents (2 equiv) in THF at –78 °C for 30 min afforded the corresponding ketones **4** and **15** in high yields (Scheme 8b). Aromatic ketone **4** was reduced with $NaBH_4$, and the resultant alcohol was directly subjected to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted cyclization/aromatization[17b] to afford 3-fluorofuran **14b** in 71% yield over two steps. Similarly, aliphatic ketone **15** was transformed into the corresponding furan **14c** in 63% yield over two steps, although heating for 48 h was required in the cyclization step. A related cyclization of amide **6ai** was also conducted upon treatment with tetra-*n*-butylammonium fluoride (TBAF) in THF at room temperature for 6 h, affording lactam **16** in 61% yield (Scheme 8c).[19]

Because 1,7-diyne **17** was readily prepared from alcohol **13**, the [2+2+2] cycloadditions of **17** were



Scheme 8. Transformations of amide moiety of **6aa** (PMP = *p*-methoxyphenyl).

next investigated (Scheme 8d). In the presence of 10 mol% Cp*RuCl(cod), **17** reacted with 1-hexyne (4 equiv) at ambient temperature to regioselectively afford the desired fused benzene **18a** in 88% yield.[20a,b] Similarly, terphenyl derivative **18b** was obtained in 73% yield when *p*-tolylacetylene was used at a reflux temperature. Furthermore, the reaction of **17** with ethyl cyanoformate afforded pyridine derivative **18c**, albeit in a moderate yield (54%).[20c,d]

Conclusion

We have developed a catalyst-free photo-coupling reaction of bromodifluoroacetamides with 1-iodoalkynes. The catalyst-free method has a wide scope for both bromodifluoroacetamides and 1-iodoalkynes with a (hetero)aromatic terminal substituents. A total of 27 coupling products were obtained in 62–83% yield, although the reaction of 1-iodoalkynes bearing a cyclohexenyl terminal substituent resulted in a lower yield of 40%. Several control experiments suggest that the present coupling proceeds via a radical chain

mechanism involving the photolysis of bromodifluoroacetamides. Subsequently, the addition of the resultant difluoroalkyl radical species to 1-iodoalkynes is followed by iodine atom elimination. The synthetic utility of the coupling products was further demonstrated by their divergent transformation into various organofluorine compounds such as trisubstituted difluoromethylalkenes, 3-fluorofurans, and fused aromatic compounds containing a difluoromethylene unit.

Experimental Section

Reaction of **1a** with **5a**: A solution of **5a** (77.7 mg, 0.318 mmol), iodoalkyne **1a** (165 mg, 0.639 mmol), and TMEDA (90 μL, 0.6 mmol) in degassed MeCN (3 mL) was stirred under irradiation (LED 448 nm, Techno Sigma PER-AMP) at room temperature under an Ar atmosphere for 5 h. The reaction was quenched by adding H_2O (20 mL) and sat. aq. $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with AcOEt (3 × 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4. The solvents were evaporated *in vacuo*, and the obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 90:1 ~ 2:1) to afford **6aa** (76.2 mg, 81%) as a colorless solid (mp 77.7–81.8 °C).

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RESEARCH ARTICLE

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