ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2024, **11**, 3072

Three-component Friedel–Crafts-type difunctionalization of ynamides with (hetero)arenes and iodine(III) electrophile†

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Received 17th March 2024,
Accepted 7th April 2024

DOI: 10.1039/d4qo00489b

rsc.li/frontiers-organic

The three-component Friedel–Crafts type functionalization of an electron-rich arene using an electrophile-activated alkyne can offer a strategy for rapidly constructing densely functionalized vinylarenes in a regio- and stereoselective fashion. An analogous process utilizing ynamides, a distinct class of electron-rich alkynes, has remained elusive despite its considerable potential for the synthesis of highly substituted and stereodefined enamides. This transformation is particularly challenging with respect to the stereochemical control, as the pivotal intermediate, the electrophile-bound keteniminium ion, can inherently undergo nucleophilic attack from either side of the cumulated double bonds. Here, we report the development of a three-component difunctionalization of ynamides with a cationic iodine(III) electrophile (benziodoxole triflate) and electron-rich (hetero)arenes that consistently displays *trans*-selectivity irrespective of the steric profiles of the ynamide and the arene. The reaction proceeds quickly under mild conditions across diverse arenes and heteroarenes, producing α-aryl-β-iodanyl enamides in a regio- and stereocontrolled manner. The robust *trans*-selectivity of this iodo(III)arylation process is attributed to the reactivity of a highly distorted keteniminium species generated from the ynamide and the iodine(III) electrophile. The iodanyl moiety in these reaction products is amenable to a variety of transition metal-mediated coupling, thereby facilitating access to a wide array of densely functionalized enamides.

Introduction

The Friedel–Crafts reaction represents one of the quintessential methods in synthetic organic chemistry, offering a robust avenue for the functionalization of electron-rich aromatic compounds.[1] Within a prototypical mechanistic framework, a carbocation generated by the protonation of an unsaturated reactant, such as an alkene or alkyne, undergoes an electrophilic attack on the arene substrate. An intriguing variant emerges when a heteroatom electrophile such as a halenium ion substitutes the proton as the activating agent, paving the way for an analogous Friedel–Crafts-type reaction involving the formation of a three-membered cyclic cationic species (*e.g.*, halonium ion). Despite the apparent simplicity of this mechanistic scenario, the practical execution of this intermolecular three-component assembly, enabling the vicinal difunctionalization of unsaturated bonds with the heteroatom electrophile alongside an arene nucleophile, has been met with sporadic success (Scheme 1A). Barluenga and coworkers reported iodoarylation of simple terminal and internal alkynes using cationic iodine(I) electrophile ($IPy_2{\cdot}BF_4$) in combination with excess HBF_4.[2] Later, Kitamura and coworkers disclosed iodoarylation utilizing the combination of molecular iodine and $PhI(OBz)_2$, where hypoiodide (IOBz) generated from these reagents served as the reactive electrophile.[3] Chu and Ellman recently developed a reaction system employing *N*-iodosuccinimide (NIS) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent to achieve iodoarylation of alkynes under mild conditions.[4] The Ellman group also demonstrated $(PhSO_2)_2NSCF_3$ as a viable sulfur-based electrophile for analogous trifluoromethylthioarylation. The *trans*-selectivity of this difunctionalization, guaranteed by the arene nucleophile's backside attack on the iodirenium ion, renders this three-component conjugation highly attractive in the context of stereocontrolled synthesis of multisubstituted olefins. This is particularly pertinent given the utility of the carbon–iodine bond in subsequent synthetic elaborations. Consequently, further development of the electrophile-mediated arylative difunctionalization encompassing broader acetylenic compounds with carbo- and heterocyclic arenes is strongly desired.[5]

Ynamides, characterized by their electron-rich and polarized C–C triple bond, have become valuable building blocks for synthesizing nitrogenous compounds like enamides and

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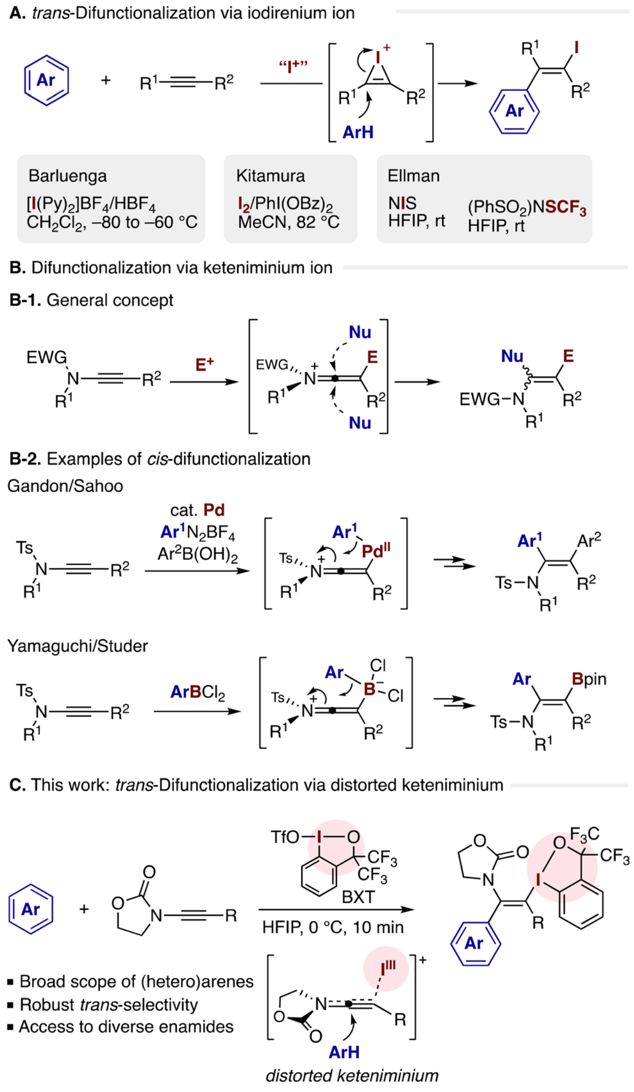
† Electronic supplementary information (ESI) available. See DOI: **https://doi.org/10.1039/d4qo00489b**



Scheme 1 Arylative difunctionalization of alkynes *via* electrophilic activation.

N-heterocycles.[6] Their unique electronic nature makes them behave distinctly from common alkynes toward electrophilic activation (Scheme 1B-1). Thus, an electrophile undergoes addition onto the distal acetylenic carbon, resulting in a keteniminium ion. Unlike electrophile-activated simple alkynes, the keteniminium species is susceptible to nucleophilic attack from either side of the cumulated double bonds, presenting a significant challenge for stereochemical control within the reaction. Addressing this challenge in the context of arylative difunctionalization, Sahoo *et al.* demonstrated an elegant solution through Pd-catalyzed *cis*-diarylation (Scheme 1B-2),[7] arylalkenylation,[8] and arylmethylation,[9] wherein a keteniminium intermediate, generated from the ynamide and an arylpalladium(II) species, undergoes intramolecular migration of the aryl group. Yamaguchi and Studer exploited analogous strategies for intramolecular aryl transfer, achieving *cis*-arylboration of ynamides with electrophilic dichloroarylboranes.[10]

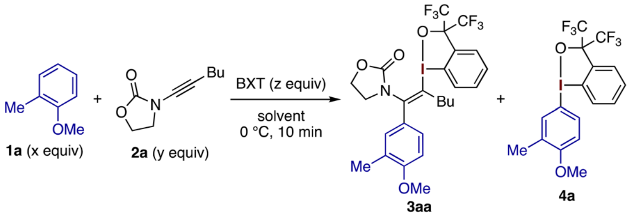
Despite these remarkable achievements employing functionalized aryl donors, the intermolecular arylative difunctionalization of ynamides using readily available unfunctionalized arenes and heteroarenes, paralleling the aforementioned iodoarylation, has remained elusive.[11,12]

Herein, we report a three-component Friedel–Crafts-type arylative *trans*-difunctionalization of ynamides using unfunctionalized (hetero)arenes and benziodoxole triflate (BXT), an iodine(III) electrophile (Scheme 1C). The reaction engages various electron-rich arenes and heteroarenes to produce α-(hetero)aryl-β-iodanyl enamides in good yields in a regio- and stereoselective fashion. DFT calculations suggested that the approach of the arene nucleophile is directed by a significantly distorted keteniminium intermediate formed between the ynamide and the bulky iodine(III) electrophile, leading to the consistently *trans*-selective difunctionalization process irrespective of the steric properties of the arene nucleophile and the ynamide substituent. The iodanyl group in the products serves as a versatile handle for further synthetic elaborations to prepare structurally diverse multisubstituted enamides. Given the use of unfunctionalized (hetero)arenes as arylating agents and the versatility of the iodanyl group, this reaction would complement the aforementioned arylative difunctionalization reactions of ynamides. Furthermore, in the context of hypervalent iodine chemistry, the present multisubstituted β-iodanyl enamides feature distinct structural patterns that are complementary to those accessible *via* hydroamidation of ethynylbenziodoxoles (EBXs)[13] or iodo(III)amidation of internal alkynes.[14]

Results and discussion

As a part of our studies on iodo(III)functionalization reactions of alkynes with iodine(III) electrophile and nucleophiles for the synthesis of vinylbenziodoxoles (VBXs),[14–17] we recently identified ynamides as excellent substrates for the *trans*-iodo(III) etherification using benziodoxole triflate (BXT) and alcohols, affording β-alkoxy-β-amido VBXs.[18] Meanwhile, we also demonstrated the capacity of BXT as a prominent electrophile for the C–H λ^3-iodanation of electron-rich (hetero)arenes.[19] Given these backgrounds, we posited that the iodine(III) electrophile could engage electron-rich (hetero)arenes as nucleophiles for the iodo(III)functionalization of ynamides, but only when the competing C–H λ^3-iodanation could be effectively suppressed. With this potential pitfall in mind, we took the oxazolidinone-containing ynamide **1a** and 1-methoxy-2-methylbenzene (**2a**) as model substrates to explore the feasibility of the desired iodo(III)arylation (Table 1). The reaction between **1a** (1.2 equiv.), **2a** (1 equiv.), and BXT (1.2 equiv.) was found to proceed smoothly in HFIP (0.2 M) at 0 °C, affording the C4-alkenylated product **3aa** in 58% yield as a single regio- and stereoisomer (entry 1). However, this reaction was accompanied by a substantial amount (27%) of the aromatic C–H iodanation product **4a**. To our delight, the chemoselectivity for **3aa** could be significantly improved by modifying

Table 1 Three-component alkenylation of 1-methoxy-2-methylbenzene (**1a**) with ynamide **2a** and benziodoxole triflate[a]



Entry	Solvent	x	y	z	Conc. [M]	**3aa**[b] [%]	**4a**[b] [%]
1	HFIP	1.2	1.0	1.2	0.20	58	27
2	HFIP	1.2	1.0	1.2	0.10	66	23
3	HFIP	1.2	1.0	1.2	0.05	74	23
4	HFIP	1.0	1.2	1.2	0.05	80	19
5	HFIP	1.0	1.5	1.5	0.05	82	17
6	HFIP	1.0	2.0	2.0	0.05	92[c]	7[c]
7	TFE	1.0	2.0	2.0	0.05	0	89
8	MeCN	1.0	2.0	2.0	0.05	0	0
9	CH_2Cl_2	1.0	2.0	2.0	0.05	0	0

[a] The reaction was performed on a 0.1 mmol scale. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.

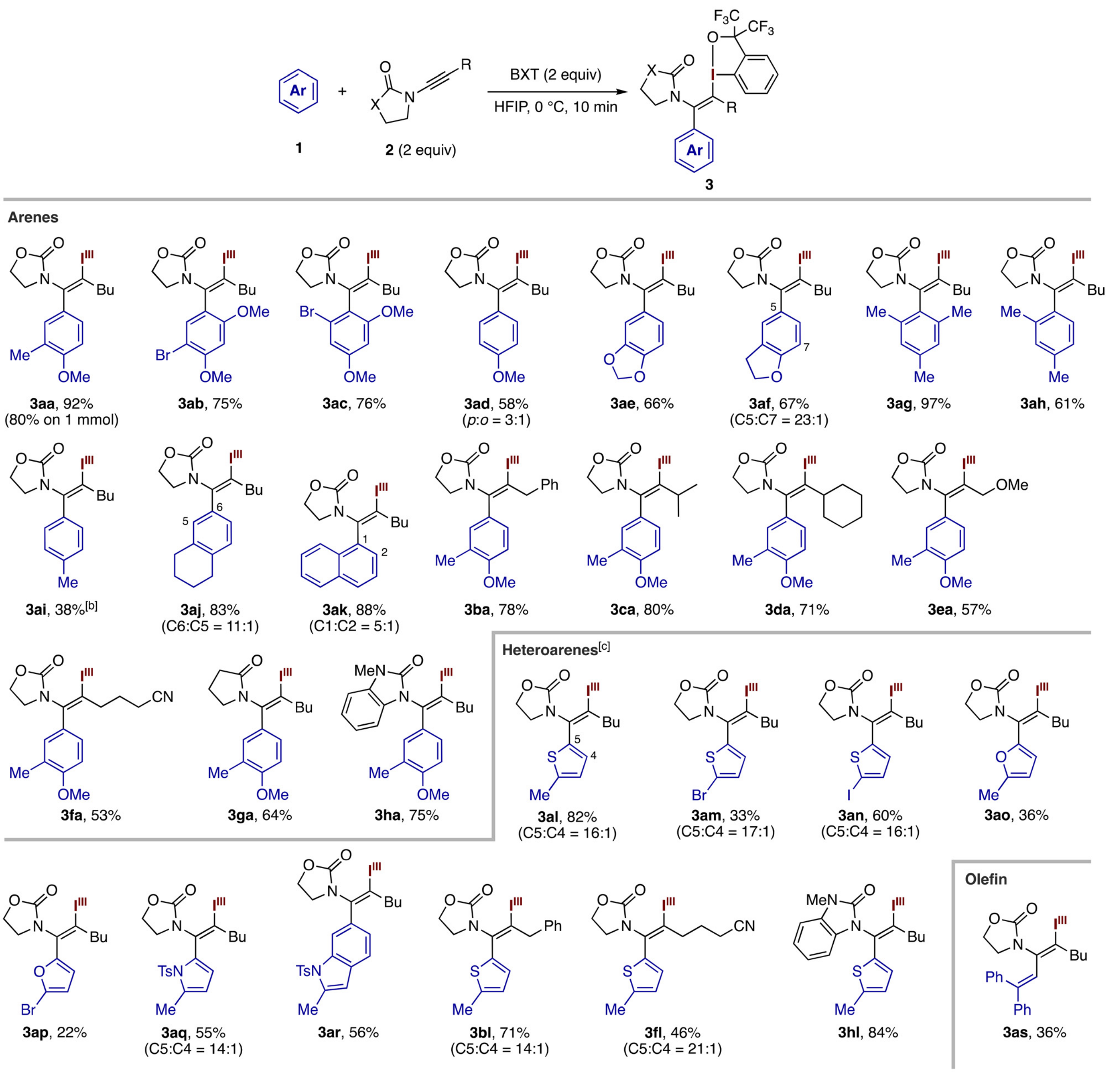
the reaction stoichiometry and the concentration (entries 2–6). The reaction using **1a** as the limiting agent and 2 equiv. each of **2a** and BXT at a lower concentration (0.05 M) was completed within 10 min, affording **3aa** in 92% isolated yield along with a much-diminished amount (7%) of **4a** (entry 6). Importantly, HFIP proved crucial for the present reaction. The reaction in analogous fluorinated alcohol, TFE, failed to produce the three-component product **3aa** but afforded a large quantity (89%) of **4a** (entry 7). Meanwhile, neither **3aa** nor **4a** was obtained in other solvents such as MeCN and CH_2Cl_2, where the formation of several unidentified products arising from **1a** and **2a** was observed (entries 8 and 9). As is commonly conceived for HFIP-facilitated Friedel–Crafts reactions,[20] we speculate that HFIP stabilizes cationic intermediates such as the iodine(III)-bound keteniminium ion and the ensuing arenium ion (see the following mechanistic discussion).

Having identified the optimized conditions, we explored the scope of the three-component coupling (Table 2). Various alkoxy-substituted arenes smoothly participated in the reaction with **2a** at the electron-rich and less hindered position to afford the enamide products **3aa–3af** in moderate to good yields. 1-Bromo-3,5-dimethoxybenzene was exclusively alkenylated at the 2-position (see **3ac**), whereas anisole afforded a mixture of *para*- and *ortho*-alkenylated products in a ratio of 3 : 1 (see **3ad**). The reaction using **1a** could be performed on a 1 mmol scale to give the product **3aa** in a respectable yield of 80%. Mesitylene, *m*-xylene, and toluene also afforded the desired products **3ag–3ai**. While sluggish, the reaction of toluene took place exclusively at the *para*-position. Tetrahydronaphthalene and naphthalene both smoothly underwent the three-component alkenylation. The former was functionalized predominantly at the C6 position (C6 : C5 = 11 : 1), while the latter preferentially reacted at the C1 position (C1 : C2 = 5 : 1). Besides **2a**, the iodo(III)arylation using **1a** tolerated oxazolidinone-based ynamides bearing benzyl, isopropyl, cyclohexyl, methoxymethyl, and cyanopropyl groups, affording the respective products **3ba–3fa** in moderate to high yields. Meanwhile, a phenyl-substituted ynamide failed to participate in the present reaction. The oxazolidinone moiety in the ynamide could be replaced by a pyrrolidinone moiety or a benzoimidazolone moiety (see **3ga** and **3ha**). Unfortunately, ynamides containing acyclic carboxamide (NMeAc) and sulfonamide (NMeTs) failed to undergo the desired iodo(III)arylation under the present conditions.

The present three-component coupling proved feasible with electron-rich heteroarenes. Using a near equimolar mixture of 2-methylthiophene (1.2 equiv.), ynamide **2a** (1 equiv.), and BXT (1.2 equiv.) under diluted conditions (0.05 M), the alkenylation took place smoothly with high regioselectivity at the C5 position over the C4 position (C5 : C4 = 16 : 1), furnishing the desired enamide product **3al** in 82% yield (see Table S1†). Notably, unlike the case of the arene **1a**, we did not observe the direct C–H iodanation of the thiophene ring as a competing side reaction. 2-Bromo- and 2-iodo thiophenes also took part in the C5-selective reaction to afford the corresponding products **3am** and **3an**, respectively. Analogous 2-substituted furan and pyrrole derivatives were also alkenylated at the C5 position, albeit in moderate yields (see **3ao–3aq**). Interestingly, 1-tosyl-2-methylindole underwent regioselective alkenylation at the C6 position rather than the expected C3 position to give the product **3ar** in 56% yield, which represents a rare selectivity case of the Friedel–Crafts reaction of C3-free indole derivatives.[21] Besides **2a**, different ynamides such as **2b**, **2f**, and **2h** smoothly underwent the reaction with 2-methylthiophene to give the desired products **3bl**, **3fl**, and **3hl** with high regioselectivity. Finally, an olefin such as 1,1-diphenylethene proved to serve as a reactant in the present three-component coupling, affording the dienamide derivative **3as** in a moderate yield. Meanwhile, other olefins such as cyclohexene and α-methylstyrene failed to participate in the reaction.

For the known electrophile-mediated Friedel–Crafts alkenylation (Scheme 1b),[2–4] the intermediacy of a three-membered cationic species (*e.g.*, iodirenium and thiirenium) is invoked to account for the *trans*-selectivity, where the arene nucleophile can only approach from the opposite side of the heteroatom electrophile. On the other hand, acid- and electrophile-mediated functionalization of ynamides is generally assumed to proceed *via* a keteniminium species having an N═C(α)═C (β) array.[6] In this case, the nucleophile can potentially approach from either side of the α-carbon, where the favorable reaction pathway would heavily depend on the relative steric size of the two substituents on the β-carbon (*cf.* Scheme 1B-1). Thus, while *cis*-addition is common in proton-mediated nucleophile addition to ynamides, high stereoselectivity would not be *a priori* guaranteed for electrophile-mediated variants. With these considerations in mind, we performed DFT calculations to gain insight into the *trans*-selectivity of the present reaction (Fig. 1a). Starting from **1a**, model ynamide **2a′**, and

Table 2 Scope of iodine(III)-mediated three-component Friedel–Crafts alkenylation of arenes and heteroarenes with ynamides[a]



[a] Unless otherwise noted, the reaction was performed on a 0.1 mmol scale under the conditions in Table 1, entry 6. The symbol I^{III} in each product refers to the benziodoxole moiety. [b] The reaction was performed using 3 equiv. (0.3 mmol) of toluene, 0.1 mmol of **2a**, and 0.1 mmol of BXT. [c] The reaction of a heteroaromatic substrate was performed using 1.2 equiv. (0.12 mmol) of the heteroarene, 0.1 mmol of ynamide, and 0.12 mmol of BXT.

BXT (ΔG = 0.0 kcal mol^{-1}), the latter two form a highly distorted keteniminium species **CP0** (ΔG = 1.2 kcal mol^{-1}) upon dissociation of the triflate anion from the iodine center. This species can engage **1a** to give rise to complexes **CP1t** or **CP1c**, where **1a** is loosely positioned around the opposite or same side of the iodanyl group at the expense of free energy of *ca.* 4–5 kcal mol^{-1}. **CP1t** proceeds to the transition state of *trans*-iodo(III)arylation, **TS1t** (ΔG = 12.6 kcal mol^{-1}), which leads to a Wheland-type intermediate **Int1t** (ΔG = −0.5 kcal mol^{-1}). Unlike the typical energy landscape of Friedel–Crafts reaction, **Int1t** is on a similar energy level as the starting materials and readily undergoes deprotonative rearomatization *via* **TS2** (ΔG = 3.1 kcal mol^{-1}) with the aid of the internal triflate, furnishing the thermodynamically stable enamide product **PD** (ΔG = −15.9 kcal mol^{-1}). The alternative *cis*-iodo(III)arylation pathway was found to be feasible, albeit with much higher activation energy (by >5 kcal mol^{-1}) *via* **TS1c** (ΔG = 17.8 kcal mol^{-1}). Note that the competing C–H iodanation of **1a** with BXT to give **4a**

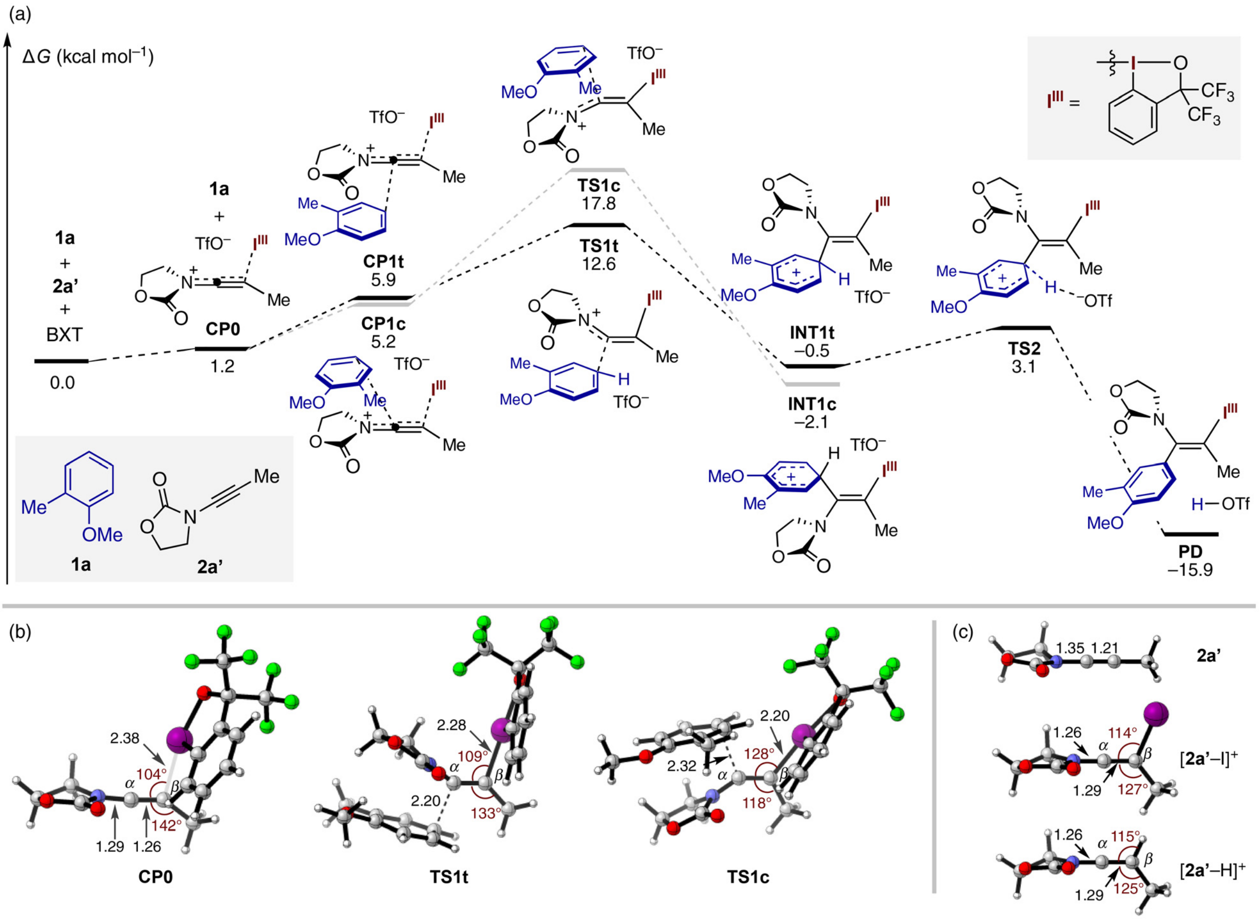
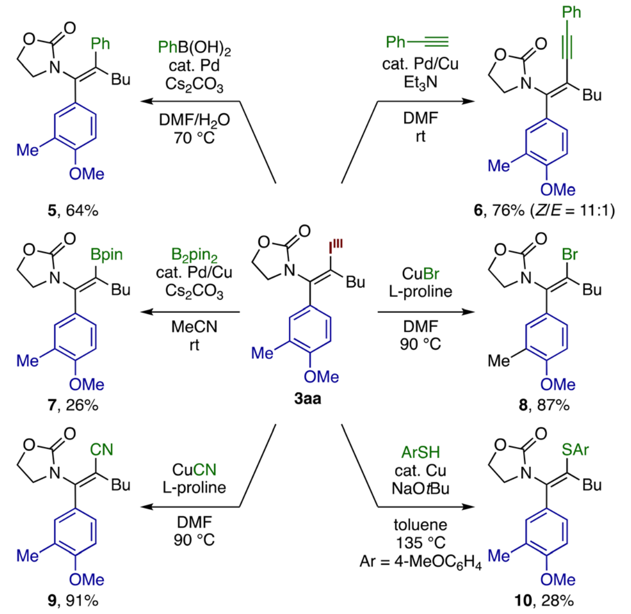


Fig. 1 (a) The energy profile and (b) the structures of the key intermediate and transition states (triflate is omitted for clarity) of three-component coupling between 1-methoxy-2-methylbenzene (**1a**), ynamide **2a'**, and BXT (M06-2X(CPCM, HFIP)/6-311+G(2df,2p)-SDD(for I)//M06-2X/6-31+G(d, p)-SDD(for I)). (c) Optimized structures of ynamide **2a'** and keteniminium ions generated from **2a'** and I^+ or H^+. Distances are in Å.

(*cf.* Table 1) was calculated to proceed with an activation energy of 19.6 kcal mol^{-1} (see the ESI†). While quantitative comparison of the three-component and two-component reactions is nontrivial, the calculated activation free energies appear consistent with the preference for the three-component reaction, especially when using the arene as the limiting substrate (*cf.* Table 1).

A close look at the intermediate **CP0** reveals its significant structural deviation from typical keteniminium geometry, with the β-carbon being far from an ideal trigonal geometry (Fig. 1b). Thus, the iodine center is significantly tilted toward the α-carbon (∠C(α)–C(β)–I = 104°), while the C(α)–C(β)–C(Me) angle (142°) is exceedingly wider than 120°. This angle distortion, along with the much longer C(β)–I length (2.38 Å) compared to the final product **PD** (2.18 Å), is suggestive of incomplete charge transfer from the ynamide to the BX cation in **CP0**. A quantum theory of atoms in molecules (QTAIM) analysis of the bond critical point between I and C(β) in **CP0** and **PD** also underlined a significantly weaker nature of the C(β)–I bonding in **CP0** (see Table S2†). The unique structural feature of **CP0** can be manifested by its comparison with keteniminium ions [**2a'**–I]$^+$ and [**2a'**–H]$^+$ generated upon attaching I^+ and H^+, respectively, to **2a'** (Fig. 1c). Thus, the distinction between these normal keteniminiums and **CP0** is reflected in their more trigonal-like β-carbons, shorter C(α)–N bonds, and longer C(α)–C(β) bonds, with which **CP0** may be formally regarded as "half-keteniminium" featuring partial C(α)–N double bond, partial C(α)–C(β) triple bond, and partial C(β)–I bond. The transition from **CP0** to the *trans*-iodo(III)arylation TS (**TS1t**) requires a relatively small degree of deformation around the β-carbon (∠C(α)–C(β)–I = 109°, ∠C(α)–C(β)–C(Me) = 133°). By contrast, to accommodate **1a** on the same side of the bulky iodanyl group while avoiding steric clash, the *cis*-iodo(III)arylation TS (**TS1c**) has to go through a significant structural deformation (∠C(α)–C(β)–I = 128°, ∠C(α)–C(β)–C(Me) = 118°). These structural features account for the robust *trans*-selectivity observed across diverse aromatic and heteroaromatic nucleophiles.

The present three-component coupling product is amenable to a variety of transition metal-mediated conversion of the C–I(III) bond (Scheme 2). Suzuki–Miyaura and Sonogashira couplings of **3aa** afforded the arylated and alkynylated enam-



Scheme 2 Product transformations. See the ESI† for the detailed reaction conditions for each transformation.

ides **5** and **6**, respectively, in good yields with retention of the stereochemistry. Miyaura borylation of **3aa** furnished the β-borylated enamide **7**,[22] albeit in a modest yield. Exposure of **3aa** to stoichiometric CuBr or CuCN resulted in efficient conversion of the iodane moiety to Br or CN group, producing the β-bromo- and β-cyano enamides **8** and **9** in excellent yields. Although sluggish, Ullmann-type C–S coupling on **3aa** also proceeded to give the β-arylthio enamide **10**. These transformations collectively demonstrate the versatility of the β-iodanyl enamides[13,14] as precursors to densely functionalized enamides, many of which would not be readily accessible by existing approaches.

Conclusions

In summary, we have developed a three-component Friedel–Crafts-type arylative difunctionalization of ynamides mediated by iodine(III) electrophile. The reaction encompasses a broad spectrum of electron-rich arenes and heteroarenes as competent nucleophiles, thus providing access to structurally diverse α-aryl-β-iodanyl enamides (or β-(hetero)aryl-β-amido VBXs) in a regio- and stereocontrolled manner. The uniform *trans*-selectivity of the reaction is ascribed to the nature of the bulky BX cation to form a distorted and incomplete keteniminium species with ynamide, which imposes distinct steric hindrances to two possible nucleophilic approaches. It is also worthwhile noting that the enamide products exhibit remarkable stereochemical integrity, undeterred by the generation of strongly acidic HOTf during the reaction, which could ostensibly cause post-reaction isomerization. The versatility of the BX group as a leaving group in the follow-up chemistry allows for converting the present products into structurally diverse, densely functionalized enamides in a stereoretentive fashion. The extension of the present three-component Friedel–Crafts chemistry to other classes of alkynes and unsaturated compounds and further exploration of iodo(III)functionalization of ynamides are underway.

Author contributions

J. K. and N. Y. conceived the project. T. N. performed and analyzed experiments with the assistance of J. K., S. I., and N. Y., J. K. performed the DFT calculations. N. Y. wrote the manuscript with the assistance of J. K. and S. I.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by JSPS KAKENHI (Grant No. 20K23375 (N. Y.) and 19K15552 (J. K.)), The Uehara Memorial Foundation (N. Y.), Research Support Project for Life Science and Drug Discovery (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED (Grant No. JP23ama121040 (N. Y.)), and the Agency for Science, Technology and Research (A*STAR) AME IRG grant (A2083c0056 (S. I.)). We thank Central Glass Co., Ltd. for the generous donation of HFIP and 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (HFAB).

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