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Cu-Catalyzed Cyclization/Coupling of Alkenyl Aldimines with Arylzinc Reagents: Access to Indole-3-diarylmethanes

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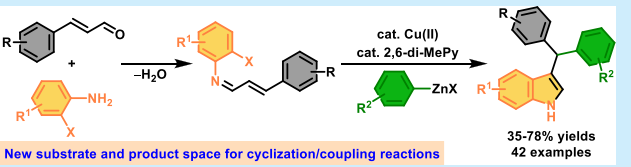
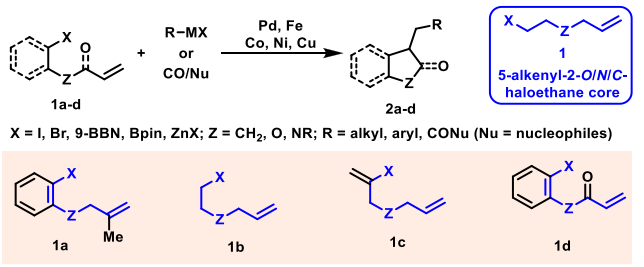
ABSTRACT: We report a Cu(II)-catalyzed cyclization/coupling of alkenyl aldimines with arylzinc reagents to create indole-3-diarylmethane derivatives (Sapkota et al. *ChemRxiv* **2022**, DOI: 10.26434/chemrxiv-2022-d6qn). The current reaction provides a unified modular route from readily available starting materials to indole-3-diarylmethanes in which all three arene cores can be decorated with differential functional substitutions on demand. Since the cyclization/coupling of alkenyl aldimines is unknown to date, the current method widens the scope with regard to both the substrate and product diversity for this class of reaction.



Transition metal-catalyzed cyclization/coupling of alkenyl halocarbons with carbon sources is a promising synthetic method to generate complex carbocycles and heterocycles rapidly from simple chemicals.[1,2] Since early disclosures,[3] a number of catalytic systems have been developed that exploited *ortho*-*N*/*O*-allyl(2-methyl)iodoarenes (Scheme 1, **1a**) as alkenyl haloarenes, and organotin and organoboron reagents as coupling partners. These Pd-catalyzed reactions involved alkyl-Pd(II) intermediates lacking β-Hs. Recently, the limitation with β-Hs has been systemically addressed by implementing catalysts derived from Co, Fe, Ni, and Cu. These metals enabled the use of *N*/*O*-allyl-haloethanes (**1b**–**c**) that proceeded via β-H-alkylmetal intermediates. For example, Oshima,[4] Kang,[5] Cárdenas,[6] Lautens,[7] ourselves,[8] and others[9] disclosed Co-, Fe-, Mn-, and Ni-catalyzed cyclization/coupling of **1a**–**c** types of substrates with aryl Grignard and alkyl/arylzinc reagents, arynes, aryl C–H bonds, and CO/*N*,*O*-nucleophiles to furnish cyclic products **2a**–**c**.

Scheme 1. Most Common Substrate Architectures for Cyclization/Coupling and the Resultant Products



Recently, Fu,[10] Brown,[11] and ourselves[12] also revealed that *N*/*O*-allyl-alkyl/arylboron and alkyl/arylzinc reagents, the class **1a**–**b** type of substrates, could undergo cyclization/coupling with aryl and alkyl halides to generate five-membered carbo- and heterocycles. The class **1a**–**b** substrates have also been elegantly demonstrated by Diao,[13] Wang,[14] Peng,[15] and others[16] to participate in Ni-catalyzed reductive cyclization/coupling with aryl halides, which furnished similar cyclic products. Lautens,[17] Kong,[18] and others[19] have ingeniously leveraged Rh-, Pd-, and Ni-catalysts for the cyclization/coupling of class **1d** substrates with arylboron reagents, aryl halides, C–H bonds, and CO/*N*,*O*-nucleophiles. Reactions that rely upon C–C and C–X (X = NR_2, SR, Cl, F) bond activation[20] and the use of enolate nucleophiles[21] have also furnished **2a**–**d** types of carbocyclic products by cyclization/coupling of alkenyl thioesters and ketones, acyl amides, and acyl halides. These cyclization/coupling methods have occasionally been interrogated to synthesize a score of bioactive and pharmaceutically relevant cyclic cores, thereby unmistakably claiming the versatility and synthetic potential of the reactions.[8,10,13a]

Despite profound interest and synthetic appeal, there is little to no attention on expanding the scope of this class of reaction. Therefore, the scope of cyclization/coupling reactions with carbon sources is so far largely confined within a relatively narrow substrate architecture and product diversity.[22] As evident from the published reports, a large majority of the reactions depend on the 5-alkenyl-2-*O*/*N*/*C*-haloethane core

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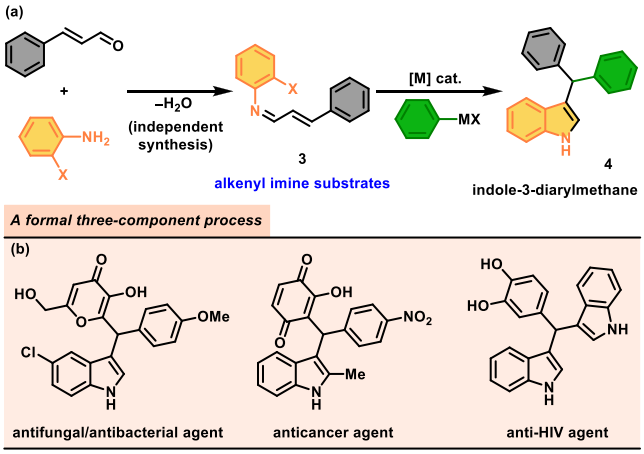
Org. Lett. 2022, 24, 6213–6218

(1) and create products with cyclopentane, pyrrolidine, and tetrahydrofuran rings. The 5-alkenyl-2-*O*/*N*/*C*-haloethane core (1) is typically derived from the products of a halohydrin reaction and *O*/*N*-acylation (Scheme 1). Herein, we introduce a new substrate strategy for cyclization/coupling in which we combine alkenyl aldehydes with anilines by dehydration to generate alkenyl aldmines (3) (Scheme 2a). We envisioned

Scheme 2. (a) This Work: Alkenyl Imines for Cyclization/Coupling Reaction; (b) Biologically Active Indole-3-diarylmethane Derivatives and Their Analogs

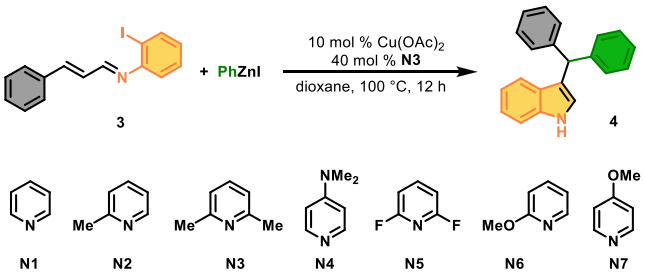


that the strategically situated alkenes in these aldimines could facilitate a metal-catalyzed cyclization to occur with the *ortho*-haloarene and, therefore, increase the repertoire of both the substrates (3) and the heterocyclic products (4) previously inaccessible by cyclization/coupling reactions.[23] C-3-substituted indoles are present in natural products[24] and are of great interest in drugs, pharmaceuticals, agrochemicals, and materials.[25] In particular, indole-3-diarylmethane derivatives (4) and their analogs are biologically active and serve as potent antifungal and antibacterial agents,[26] topoisomerase I inhibitors (anticancer agents),[27] and HIV-1 integrase inhibitors (Scheme 2b).[28]

To interrogate the feasibility of using alkenyl imines for cyclization/coupling, we synthesized *N*-(2-iodophenyl)-cinnamaldimine (3, X = I) through the condensation of 2-iodoaniline with cinnamaldehyde. Examination of different reaction parameters for the reaction of the aldimine **3** with PhZnI revealed that 10 mol % $Cu(OAc)_2$ effected the cyclization/coupling and furnished *N*-unprotected indole-3-diphenylmethane **4** in 72% yield in the presence of 40 mol % 2,6-dimethylpyridine (**N3**) at 100 °C in 12 h (Table 1, entry 1). The reaction also proceeded in the absence of **N3**, although the indole product **4** was generated in much lower yield (35%) (entry 2). Evaluation of other pyridine derivatives showed that 3-methylpyridine (**N2**) and 4-dimethylaminopyridine (**N4**) increased the product yields to 53−55% (entries 4−5), while others (**N1**, **N5**−**N7**) had zero to minimal effects in the reaction (entries 3, 6−8). The indole **4** was formed in lower yields in solvents other than dioxane (entry 9). Catalysts based on other metals, such as Pd, Fe, Co, and Ni, generated zero to trace amount of the indole **4** and mostly produced biaryls from direct cross-coupling (entry 10).[29]

After optimization of the reaction parameters, we examined the scope of the reaction for arylzinc reagents (Scheme 3). The reaction furnished indole derivatives in good yields with both

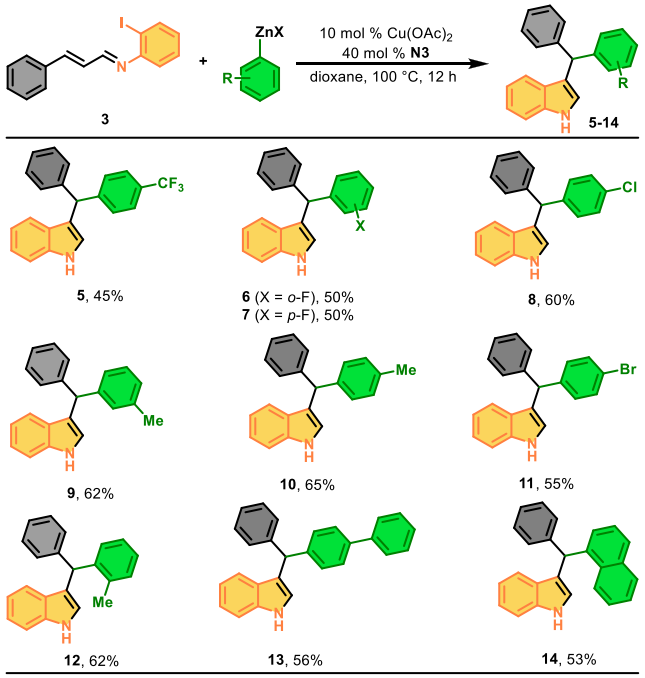
Table 1. Optimization of Reaction Parameters[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	72 (64)
2	without **N3**	35
3	**N1** instead of **N3**	38
4	**N2** instead of **N3**	53
5	**N4** instead of **N3**	55
6	**N5** instead of **N3**	31
7	**N6** instead of **N3**	38
8	**N7** instead of **N3**	25
9	THF, NMP, DMF, DMSO, or toluene instead of dioxane	9−20
10	Pd-, Fe-, Co-, and Ni-salts instead of $Cu(OAc)_2$[c]	0−5

[a]Reactions were conducted in 0.10 mmol scale with 2.0 equiv of PhZnI in 0.5 mL of solvent. [b]^{1}H NMR yields using pyrene as a standard. The number in parentheses is the isolated yield from a 0.50 mmol scale reaction in 2.5 mL of dioxane. [c]10 mol % of $FeBr_3$, $Ni(cod)_2$, $NiBr_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $Co(acac)_2$ were used.

Scheme 3. Scope of the Reaction with ArZnI[a]



[a]Reactions were conducted in 0.50 mmol scale with 2.0 equiv of ArZnI in 2.5 mL of dioxane. Reported is the % yields of isolated products.

electron-rich and electron-poor arylzinc reagents (**5**−**10**), and tolerated functional groups such as trifluoromethyl, fluoro, chloro, and methyl. Arylzinc reagents bearing reactive bromide and sterically hindered *ortho*-Me groups were tolerated, which afforded indole products in good yields (**11**, **12**). Similarly, the

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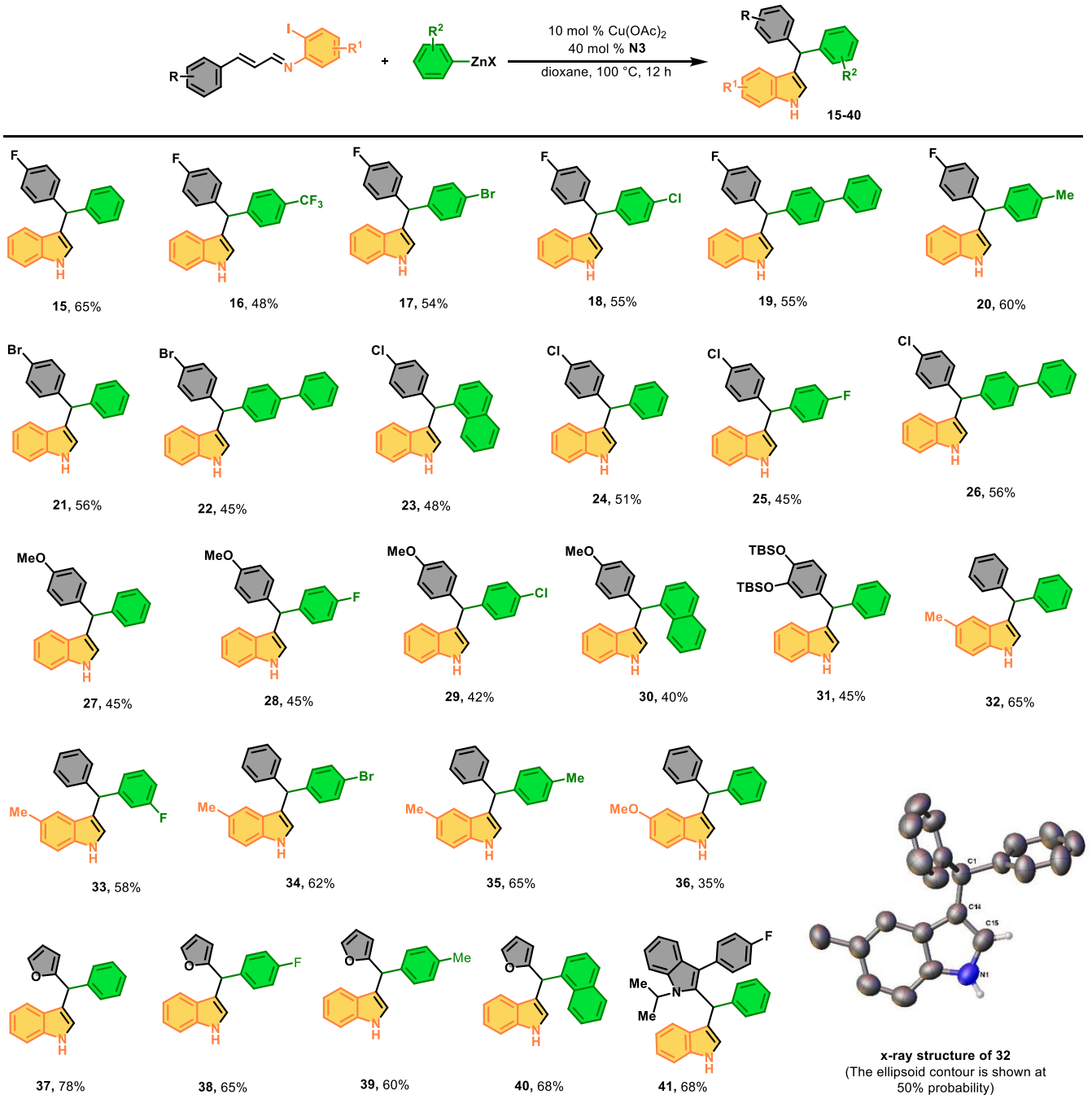
Org. Lett. 2022, 24, 6213−6218

Scheme 4. Scope of the Reaction of the Cinnamaldehyde and Aniline Components of Alkenyl Aldimines with ArZnI[a]



[a]Reactions were conducted in 0.50 mmol scale with 2.0 equiv of ArZnI in 2.5 mL dioxane. Reported % is the yields of isolated products.

reaction could also be conducted with biaryl- and 1-naphthylzinc reagents to increase the polyaromatic backbones on the indole core (**13**, **14**).

We also examined the scope of the reaction with substitutions on the cinnamaldehyde and aniline, the two components of the alkenyl imines (Scheme 4).[30] The alkenyl imines derived from 2-iodoaniline and cinnamaldehyde bearing fluoro, bromo, and chloro could readily undergo cyclization/coupling with arylzinc reagents containing trifluoromethyl, fluoro, bromo, chloro, phenyl, and 1-naphthyl groups (**15**–**26**). The alkenyl imines with cinnamaldehyde unit containing an electron-donating group, such as methoxy and OTBS, could also be used for cyclization/coupling with phenyl, 4-fluorophenyl, 4-chlorophenyl, and 1-naphthylzinc iodides (**27**–**31**). The reaction was also compatible with substituted anilines bearing methoxy and methyl substituents, the alkenyl imines of which generated products in good yields with phenyl, 3-fluoro, 4-bromo, and 4-methylzinc iodides (**32**–**36**). These combinations of reagents enabled us to synthesize indole-3-diarylmethane derivatives in which all three arene moieties are differently substituted.

The reaction also tolerated heterocycles on the cinnamaldehyde unit (Scheme 4). As demonstrated by the cyclization/coupling of the alkenyl imine derived from 3-(2-furanyl)-

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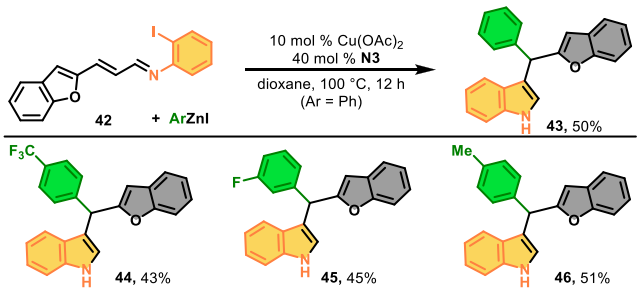
Org. Lett. 2022, 24, 6213−6218

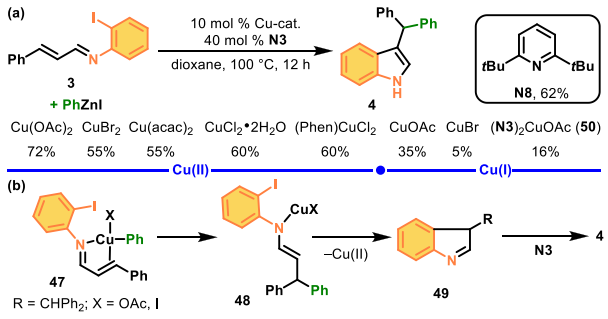
acrylaldehyde and 2-iodoaniline, the indole-3-(2-furanyl)-arylmethane derivatives were generated in good to excellent yields with phenyl, 4-fluorophenyl, 4-methylphenyl, and 2-naphthylzinc iodide (**37**−**40**). More importantly, the reaction also furnished a *C*-2/*C*-3 bis-indolyl-3-arylmethane derivative (**41**) in excellent yield by the cyclization/coupling of alkenyl imine composed of a 3-(1*H*-indol-2-yl)acrylaldehyde derivative and 2-iodoaniline with phenylzinc iodide. *C*-2/*C*-3 bis-indolylmethane is an important precursor for heterocyclic natural products such as indolocarbazoles.[31] This class of compound is also best known for mediating the toxicity of dioxin and related toxins.[32] In order to further demonstrate the scope, we also synthesized 3-(benzofuran-2-yl(phenyl)-methyl)-1*H*-indole (**43**), a potential autophagy inducer in cervical cancer cells,[33] and its three derivatives (**44**−**46**) (Scheme 5).

Scheme 5. Synthesis of Bioactive 3-Diarylmethylindole Derivatives Having Anticancer Properties



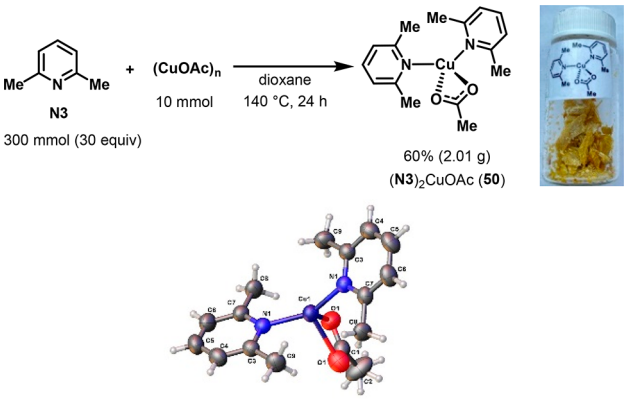
Additionally, our preliminary studies indicate that the reaction is catalyzed by a Cu(II) catalyst unbound to **N3**. Examination of various Cu(II)-salts containing different anions (OAc, Br and Cl) showed that the product **4** was formed in high yields (55−72%) (Scheme 6a). In contrast, Cu(I)-salts

Scheme 6. Control Experiments and Proposed Cyclization Steps



containing the same anions (OAc and Br) furnished the product **4** consistently in low yields (5−35%). We also synthesized a **N3**-bound CuOAc complex **50** in gram-scale (2.01 g) from the reaction of **N3** base with CuOAc in dioxane at 140 °C (Scheme 7). The structure of the complex **50** was confirmed as a tetrahedral κ^2-acetato-(**N3**)$_2$CuOAc by a single crystal X-ray crystallography. The use of the complex **50** as a catalyst under the standard conditions generated the indole product **4** only in 16% yield (Scheme 6a), further suggesting that Cu(I) is less likely to be an active catalyst. Additional experiments with (phen)$CuCl_2$ as a catalyst and the replacement of **N3** with 2,6-di-*tert*-butylpyridine (**N8**), which

Scheme 7. Synthesis of (N3)$_2$CuOAc (50) and Its X-ray Structure[a]



[a]Selected bond lengths (Å) and angles (deg): Cu1−O1, 2.340(4); Cu1−N2, 1.990(4); O1−Cu1−O1^1, 55.6(2); O1−Cu1−N2, 107.40(15); O1−Cu1−N2^1, 105.14(15). The ellipsoid contour is shown at 50% probability.

produced the indole product **4** in 60% and 62%, respectively, indicated that the reaction was catalyzed by a Cu(II) catalyst that is not bound to **N3** and that **N3** and **N8** possibly functioned as sterically hindered bases.[34]

Based on these experiments, we propose that the reaction is initiated by a Cu(II)-catalyzed conjugate addition of ArZnX to the α,β-unsaturated imine, followed by iodine atom abstraction upon single electron transfer from the Cu(II)-enamido species **48** to the intramolecular ArI (Scheme 6b). Upon cyclization of the aryl iodide onto the enamido alkene, 3*H*-indole (**49**) is released and the Cu(II) catalyst is regenerated. The 3*H*-indole is then isomerized by the **N3** base to form the final 1*H*-indole **4**.

In summary, we have developed a Cu(II)-catalyzed cyclization/coupling of alkenyl aldimines, derived from alkenyl aldehydes and anilines upon dehydration, with arylzinc reagents in a formal three-component fashion. The reaction is assisted by substoichiometric amounts of 2,6-dimethylpyridine (**N3**), which functions as a base. This cyclization/coupling reaction produces in a single step a variety of indole-3-diarylmethane derivatives, an important class of bioactive scaffolds and precursors to many heterocyclic natural products. We anticipate that the current work creates a new direction and stimulate future research in the realm of cyclization/coupling by expanding its scope to aldehydes, anilines, and arylzinc reagents, which are some of the most common and readily available precursors in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02531.

Experimental procedures and characterization data for all compounds (PDF)

Accession Codes

CCDC 2145421 and 2145423 contain 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

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Notes

The authors declare no competing financial interest.

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