Stereoselective Synthesis of *E*- and *Z*-Isocyanoalkenes

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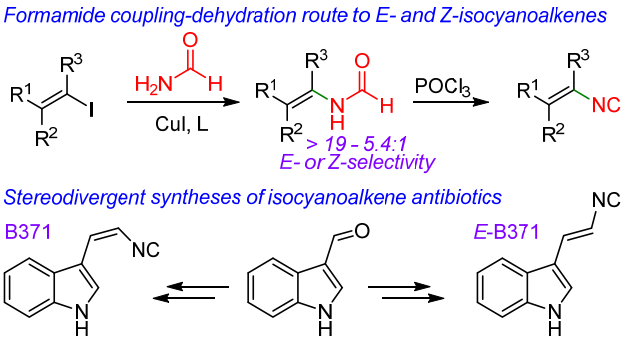
Supporting Information Placeholder



ABSTRACT: *E*- and *Z*-isocyanoalkenes were selectively synthesized via the sequential cross coupling of vinyliodides with formamide followed by dehydration. The optimal catalyst, generated in situ from Cu(I)I and *trans*-*N,N'*-dimethylcyclohexyldiamine, rapidly coupled *E*- or *Z*-vinyl iodides with formamide which minimized the isomerization of the resultant vinyl formamide. The method efficiently provided a range of acyclic, carbocyclic, and heterocyclic isocyanoalkenes; the versatility is illustrated with the selective, stereodivergent syntheses of the diastereomeric isocyanoalkene antibiotics, B371 and *E*-B371.

Isocyanoalkenes are extremely valuable functionalities that serve as lynchpins in heterocycle synthesis,[1] acceptors in radical cascades,[2] probes in bioorthogonal reactions,[3] and impart distinct bioactivities in natural products[4] and pharmaceutical leads.[5] The structural complexity of isocyanoalkenes varies tremendously as illustrated in a representative array of bioactive naturally occurring isocyanoalkenes **1**-**5** (Figure 1): the antibiotic isocyanoindole B371 (**1**)[6] and the geometric isomer **2**;[7] the *bis*-isocyanide Xanthocillin X (**3**), a potent antibiotic from *Penicillium notatum*;[8] the tricyclic anti-malarial isocyanocloven (**4**)[9] and the tetracyclic anti-fungal agent welwitindolinone A (**5**).[10] In each case the isocyanide functionality is an important pharmacophore.[5]

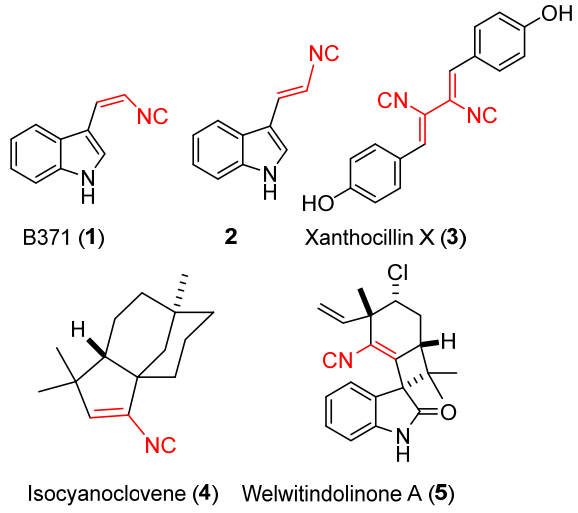
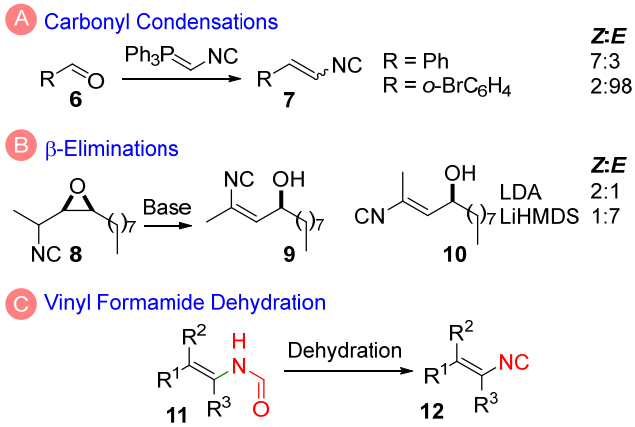


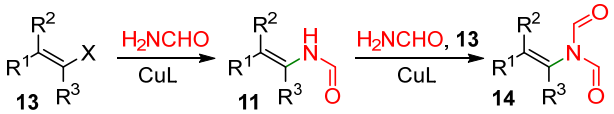
Figure 1. Representative bioactive isocyanoalkene natural products.

Stereoselective access to *E*- and *Z*-isocyanoalkenes is challenging on two fronts: the delicate carbene-like isocyanide tolerates a limited suite of reagents while the small, cylindrical isocyanide, a mere one eighth the size of a methyl group,[11] exerts minimal influence in controlling the *E*/*Z* geometry in olefin-forming reactions. [12] Of the three general routes to isocyanoalkenes (Scheme 1), traditional phosphorous ylide condensations typically afford geometric isomers unless the carbonyl is sterically biased (Scheme 1, A).[13] Isocyanoalkenes generated by base-induced β-eliminations usually have modest *E*/*Z*-ratios that are often highly sensitive to small changes in the reaction conditions (Scheme 1, B).[14] Access to isocyanoalkenes via vinyl formamide dehydration is excellent for cyclic formamides but undeveloped with acyclic vinyl formamides, probably because selectively accessing *E*- and *Z*-vinyl formamides is challenging (Scheme 1, C).[15]



Scheme 1. The three general approaches to isocyanoalkenes.

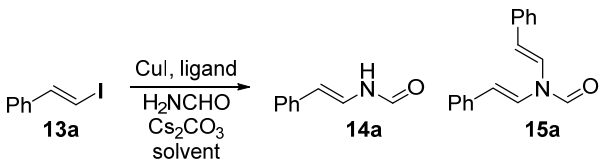
Despite the successful coupling of vinyl halides with primary and secondary amides,[16] the analogous coupling with formamide is undeveloped. Two precedents implied that geometrically defined isocyanoalkenes might be generally accessible by stereoselective coupling of a vinyl halide with formamide (**13** → **11**) followed by dehydration (Scheme 2): one example in the context of a med-chem campaign[17] and the other as an intermediate during an oxazole synthesis.[18] The attraction of a formamide coupling route to isocyanoalkenes lies in the numerous routes to the requisite *E*- or *Z*-vinyl halide precursors.[19] The challenge in coupling formamides is their lower reactivity compared to primary and secondary amides that may lead to a second, more favorable coupling of the initial product **11** → **14**,[17] and the need to prevent enamide isomerization both during[17] and following the coupling.[20]



Scheme 2. Potential formamide couplings with vinyl halides.

Exploratory forays to couple formamide with a vinyl halide (Table 1) built on detailed studies showing the efficacy of copper(I) complexes in DMF with bidentate nitrogenous ligands that mitigate catalyst deactivation caused by multiple ligation to nitrogenous ligands. [21]An initial lead was found in coupling *trans*-β-bromostyrene (**13**, R^1 = Ph, R^2 = R^3 = H, X = Br) with formamide using a catalyst formed in situ from copper iodide and *N,N′*-dimethylethylenediamine (DMEDA).[22] While the coupling of formamide with *trans*-β-bromostyrene either stalled or, under forcing conditions gave complex reaction mixtures, the analogous coupling with the more reactive *trans*-β-iodostyrene (**13b**) led to complete conversion to vinyl formamide **14a** (Table 1, entry 1). The use of proline or bipyridine as ligands were less effective (Table 1, compare entry 1 with entries 2 and 3) whereas *N,N′*-dimethylcyclohexyldiamine (DCD) gave complete conversion to vinyl formamide **14a** (Table 1, entry 4). A solvent screen with Cu(I)I and DMEDA indicated DMF to be more effective than THF (Table 1, compare entry 1 with entry 5) but isolation of the vinyl formamide from DMF proved particularly difficult; the isolated yield was 41%. Further scrutiny of solvents revealed the coupling in dioxane to be as efficient as in DMF but with a significantly easier isolation protocol (Table 1, entry 6). However, considerable *bis*-vinylformamide **15a** was generated in dioxane. The simple expedient of using excess formamide minimized the formation of **15a** allowing the facile isolation of **14a** in 68% yield (Table 1, compare entry 9 with entries 7 and 8).

Table 1. Optmization of the Isocyanosalkene Vinyliodide-Formamide Coupling

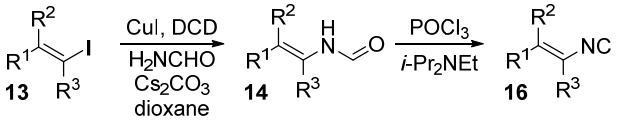


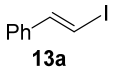
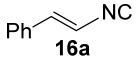
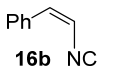
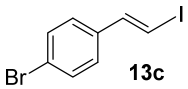
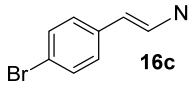
entry	ligand	solvent (formamide equiv)	T/time (°C/h)	conversion to, or yield of, **14a**
1	DMEDA	DMF (6)	85/3	100%[a]
2	proline	DMF (6)	85/6	13%[a]
3	bipyridine	DMF (6)	85/6	0%[a]
4	DCD	DMF (6)	85/6	100 [a]
5	DMEDA	THF (6)	67/24	12%[a]
6	DMEDA	dioxane (6)	85/7	41%[b]
7	DMEDA	dioxane (6)	105/3	46%[b]
8	DMEDA	dioxane (12)	105/1	47%[b]
9	DMEDA	dioxane (16)	105/5	68%[b]

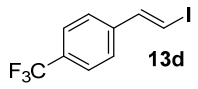
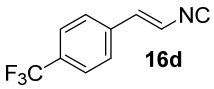
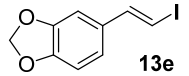
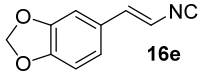
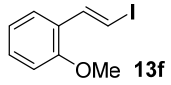
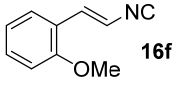
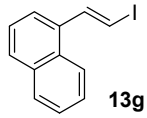
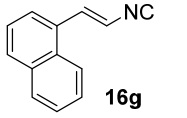
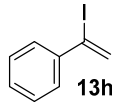
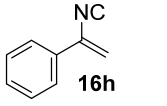
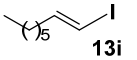
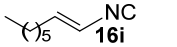
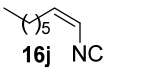
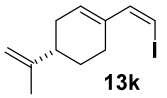
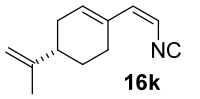
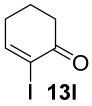
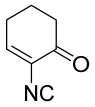
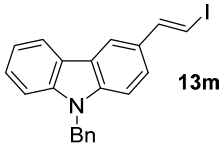
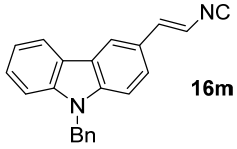
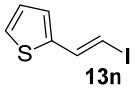
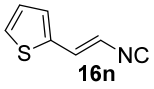
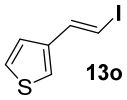
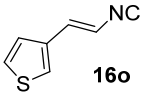
[a] Conversion. [b] Accompanied by the divinylformamide **15**.

Armed with what seemed to be the optimized conditions [Cu(I)I, DMEDA, dioxane], the coupling was performed with *cis*-β-iodostyrene **13b** (Table 2). Unfortunately, while the formamide coupling with *cis*-β-iodostyrene **13b** was efficient (62% yield) the reaction afforded primarily the *E*-vinyl formamide **14a** (*E/Z* ratio of 31:1); close monitoring of the reaction identified the problem as *E/Z* isomerization of the vinyl formamide under the reaction conditions. Switching the amine from DMEDA to DCD afforded a more reactive catalyst that decreased the coupling time from 6 h to 40 min which reduced the isomerization to afford a 19:1 *Z/E* ratio of **14b** : **14a** (Table 2, entry 2). Applying the same procedure to the *E*-β-iodostyrene **14a** afforded only one detectable geometric isomer (Table 2, entry 1). Analogous couplings with a suite of electronically diverse 2-iodovinyl arenes **13c-13g** efficiently afforded the corresponding formamides with *E/Z*-ratios greater than 19:1 (Table 1, entries 3-6); the purified formamides were dehydrated with complete retention of configuration to afford isocyanoalkenes **16c-16g**.[23] The Cu(I)I- DCD combination cleanly converted the 1,1-disubstituted alkene **13h** into the isocyanide **16h** (Table 2, entry 8). A representative series of aliphatic *E*- and *Z*-vinyl iodides **13i-13m** coupled efficiently and uneventfully with formamide (Table 2, entries 9-13); the coupling of the α-iodoenone **13m** was uneventful but the dehydration gave the rather delicate isocyanide **16m** whose isolation was only efficient when purified on silanized silica gel.[24] Heterocycles **13n-13p** coupled efficiently, though both the thiophene formamides were prone to *E/Z* isomerization that was minimized by terminating the reaction immediately upon completion (Table 2, entries 14-15). The *E*- and *Z*-vinyl formamides were separated and the major isomers were dehydrated to afford geometrically pure isocyanoalkenes **16n** and **16o**, that latter of which is an antimicrobial agent.[25]

Table 2. Coupling and Dehydration to Isocyanoalkenes

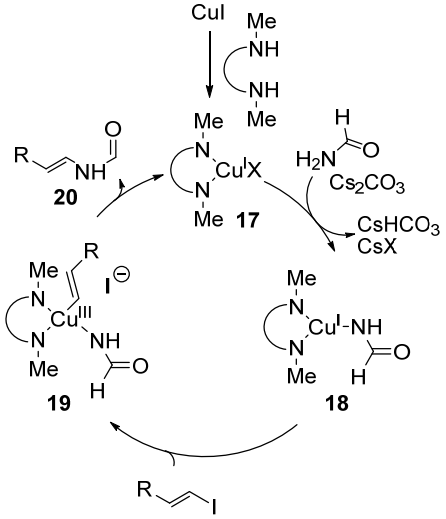


entry	vinyliodide	isocyanoalkene	yield[a]
1	 **13a**	 **16a**	74%[b] >19:1 78%
2	 **13b**	 **16b**	76% 19:1 65%
3	 **13c**	 **16c**	59% >19:1 82%

4	 **13d**	 **16d**	65% >19:1 63%
5	 **13e**	 **16e**	60% >19:1 72%
6	 **13f**	 **16f**	69% >19:1 76%
7	 **13g**	 **16g**	60% >19:1 76%
8	 **13h**	 **16h**	54% 59%
9	 **13i**	 **16i**	74% >19:1 59%
10	 **13j**	 **16j**	87% >19:1 54%[c]
11	 **13k**	 **16k**	76% >19:1 59%
12	 **13l**	 **16l**	56% 77%
13	 **13m**	 **16m**	52% >19:1 83%
14	 **13n**	 **16n**	59% 8.4:1 62%
15	 **13o**	 **16o**	63% 5.4:1 88%

[a] Yield and geometric ratio for the coupling, respectively; the second yield is for the dehydration. [b] The reaction was performed on a 2.2 mmol scale. [c] The volatility of the isocyanoalkene likely diminished the yield.

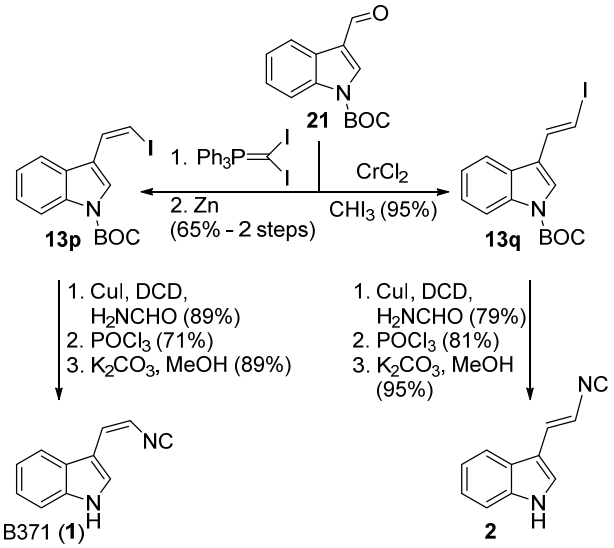
The mechanism of copper-catalyzed amide couplings involve the sequential ligation and union of formamide with the vinyl iodide (Scheme 3).[16] Complexation of formamide to catalyst **17** formed in situ from CuI and a diamine, activates the amide for deprotonation by Cs_2CO_3 to give the copper(I) amidate **18**. The precise sequence for the coupling may involve halogen abstraction or single electron transfer via radical intermediates, or an oxidative addition followed by a reductive elimination **18** → **19** → **20**.[26] Reaction monitoring indicated that the coupling occurred with retention at the sp^2 carbon suggesting either a rapid rebound of a radical intermediate before radical inversion or a retentive oxidative addition process.



Scheme 3. Potential formamide coupling mechanism.

The versatility of formamide coupling-dehydration was illustrated in the stereodivergent syntheses of two *E/Z*-diastereomeric antibiotics, B371 (**1**)[25] and the geometric isomer **2** (Scheme 4).[27] The *Z*-selective iodomethylenation of *N*-Boc-indolecarboxaldehyde **21**[28] was performed via formation the diiodoalkene followed by reduction with zinc to afford **13p** because the direct iodomethylenation with iodomethylene triphenylphosphine only afforded a 3:1 *Z/E* ratio of diastereomers.[29] The formamide coupling gave a 12.4:1 *Z/E* ratio of formamides (89%) that were separated, dehydrated (71%) and deprotected, with methanol (89%) to afford B371 (**1**).

Formation of the diastereomeric isocyanoindole **2** required the synthesis and coupling of the *E*-vinyl iodide **13q**. Iodoolefination of **21** with $CrCl_2$ and iodoform afforded a 6.2:1 ratio of *E/Z* isomers **13q**:**13p** whose coupling with formamide afforded a 79% yield of a sensitive vinyl formamide (3% erosion of configuration during coupling) that was purified to afford a single geometric isomer, dehydrated, and treated with methanolic K_2CO_3[30] to afford the isocyanovinylindole **2**.



Scheme 4. Syntheses of diastereomeric isocyano-indole antibiotics.

The long-standing challenge of selectively accessing *E*- and *Z*-isocyanoalkenes is addressed through a stereoselective, copper-catalyzed coupling of vinyl iodides with formamide followed by dehydration. The catalyst generated in situ from Cu(I)I and *N,N′*-dimethyldicyclohexyldiamine provides a rapid coupling that minimizes base-promoted isomerization of the vinyl formamide; the subsequent dehydration faithfully translates the vinyl formamide geometry to the corresponding *E*- or *Z*-isocyanoalkenes. The efficacy of the coupling-dehydration strategy was demonstrated through the stereodivergent synthesis of the diastereomeric *E/Z* isocyanoalkenylindole antiobiotics B371 (**1**) and the *E*-geometric isomer **2**.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study is available in the published article and online as Supporting Information.

Supporting Information

The data underlying this study are available in the published article and in the online supplementary material. The Supporting Information is available free of charge. Experimental procedures, compound characterization, copies of NMR spectra (PDF), and FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds **14a-p**, **16a-p**, **17**, **18**, **19**, **1**, and **2** (ZIP).

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Author Contributions

All authors made intellectual contributions to the research described in the manuscript with all the authors having approved the final version of the manuscript.

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