Heterocycle Synthesis

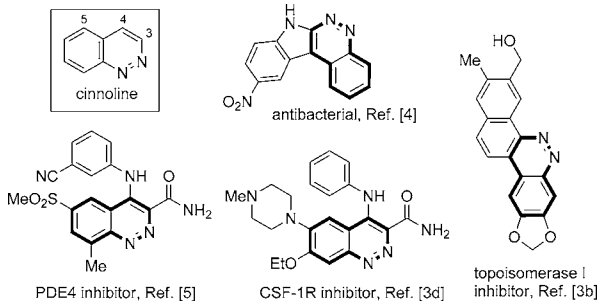
DOI: 10.1002/ange.201201529

Copper-Catalyzed Tandem C–N Bond Formation: An Efficient Annulative Synthesis of Functionalized Cinnolines**

*Catherine J. Ball, Jeremy Gilmore, and Michael C. Willis**

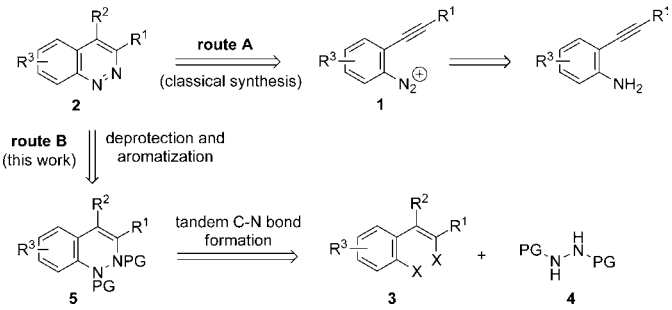
Transition metal-catalyzed aryl C–N bond formation[1] has become an important tool in the synthesis of heterocycles.[2] Mild conditions, readily accessible starting materials and user-friendly procedures are among the advantages that such a strategy offers compared to classical syntheses. However, the development of general and flexible routes to a wider variety of heterocycles remains an important goal.

Cinnolines, and cinnoline derivatives, are known to exhibit anti-cancer,[3] fungicidal and bactericidal,[4] and anti-inflammatory[5] activity as well as luminescent and optical properties (Scheme 1).[6] Yet these structures remain relatively unfamiliar in modern-day organic chemistry; when compared with their quinoline isostere, the cinnoline substructure is considerably less exploited. However, in a number of cases where the pharmacological profiles of these two structures have been directly compared, the cinnoline analogue has often exhibited superior properties.[3d,5,7] Given the promising biological profile of many cinnolines it is puzzling that these structures have not been explored more thoroughly. One reason for this is presumably the lack of efficient and accessible synthetic routes. In this Communication, we address this issue and report an efficient and flexible cinnoline synthesis based on a tandem copper-catalyzed annulation that employs a simple hydrazide nucleophile.



Scheme 1. Cinnoline and representative biologically active analogues.

Cinnolines are classically formed using cyclization of a phenyldiazonium ion onto an *ortho* functionality.[8] In the classic von Richter synthesis[9] this cyclization involves an activated *ortho*-alkyne (**1**→**2**, route A in Scheme 2). However, such a route usually presents significant limitations; strongly acidic conditions are required, potentially unstable and difficult to handle diazonium intermediates are needed, and the construction of the cinnoline framework necessarily results in substitution at the 4- and often 3-positions. Extensive transformations and harsh reaction conditions are often required to produce cinnolines lacking these substituents.[10] Alternative routes to cinnolines include cyclizations involving aryl hydrazones,[11] aryl hydrazines,[12] and nitriles,[13] and intermolecular cycloadditions.[14] However, none of these routes represent a general synthesis or allow for complete control of the substituent pattern incorporated.



Scheme 2. Retrosynthetic routes for cinnoline formation. PG = protecting group.

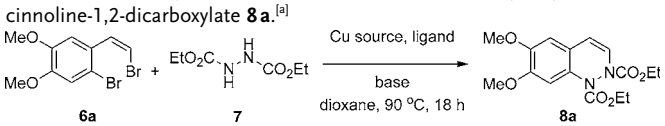
We have previously demonstrated that 2-(2-haloalkenyl)-aryl halides **3** can serve as useful precursors to a number of heterocycles, using two sequential transition metal-catalyzed reactions. For example, tandem aminations, the first intermolecular, the second intramolecular, provide efficient routes to a range of *N*-functionalized indoles.[15] An aminocarbonylation step can also be incorporated to produce quinolones and isoquinolones.[16] Benzofurans have also been prepared using related chemistry.[17] Given the versatility of these difunctionalized backbones we envisaged that they could also provide an efficient synthetic route to cinnolines. Our proposed route involved the catalytic annulation of aryl-alkenyl dihalides **3** with an *N*,*N*′-disubstituted hydrazide nucleophile **4** to provide a dihydrocinnoline derivative **5**, which could then be simply converted to the corresponding aromatic core (route B in Scheme 2).

[*] C. J. Ball, Dr. M. C. Willis
Department of Chemistry, University of Oxford, Chemistry Research Laboratory
Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: michael.willis@chem.ox.ac.uk
Homepage: http://mcwillis.chem.ox.ac.uk/MCW/Home.html
Dr. J. Gilmore
Lilly Research Centre, Eli Lilly and Company Ltd.
Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH (UK)

[**] This work was supported by the EPSRC and Eli Lilly.

Supporting information for this article (experimental details) is available on the WWW under http://dx.doi.org/10.1002/anie.201201529.

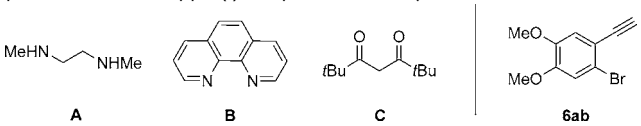
Table 1: Reaction optimization for the formation of diethyldihydrocinnoline-1,2-dicarboxylate **8a**.[a]



6a + **7** → **8a**

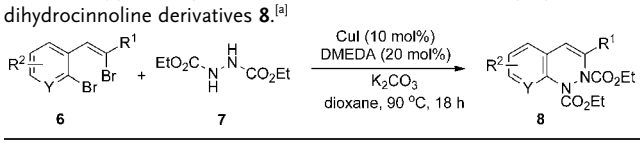
Entry	Cu source [mol%]	Ligand	Metal:Ligand	Base	Yield[b]
1	CuI [10]	**A**	1:2	K_3PO_4	54%
2	CuI [10]	**A**	1:2	Cs_2CO_3	79%
3	CuI [10]	**A**	1:2	K_2CO_3	95%
4	CuI [10]	**A**	1:2	NaO*t*Bu	0%[c]
5	CuI [10]	**B**	1:2	K_2CO_3	31%
6	CuI [10]	**C**	1:2	K_2CO_3	72%
7	CuTC [10]	**A**	1:2	K_2CO_3	82%
8	$Cu(OTf)_2$.PhH [10]	**A**	1:2	K_2CO_3	87%
9	CuI [10]	**A**	1:1	K_2CO_3	79%
10	CuI [5]	**A**	1:2	K_2CO_3	61%

[a] Reaction conditions: dihalide (1.0 equiv), diethyl-1,2-hydrazinedicarboxylate (2.0 equiv), base (2.5 equiv), dioxane, 90°C, 18 h. [b] Yield of isolated product. [c] Aryl alkyne **6ab** was isolated as the sole reaction product. CuTC = copper(I) thiophene-2-carboxylate.

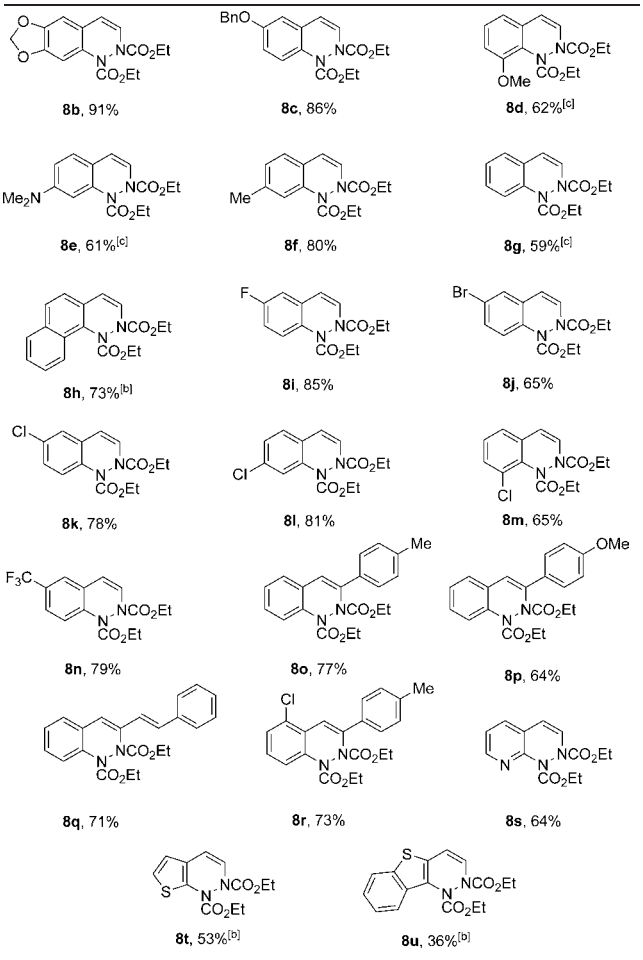


A **B** **C** **6ab**

Table 2: Copper-catalyzed tandem C–N annulation for the preparation of dihydrocinnoline derivatives **8**.[a]



6 + **7** → **8**



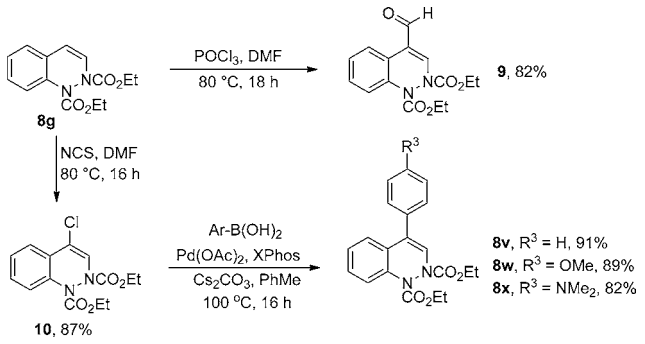
[a] Conditions: dihalide (1.0 equiv), diethyl-1,2-hydrazinedicarboxylate (2.0 equiv), CuI (10 mol%), ligand **A** (20 mol%), K_2CO_3 (2.5 equiv), dioxane, 90°C, 18 h. Yields of isolated product. Substrates were obtained with $Z{:}E > 10{:}1$, except in cases [b] where this was markedly lower. See Supporting Information for details. [c] Using aryl chloride substrate.

Our initial investigations to realize this novel route to cinnolines focused on the combination of 2-(2-bromoalkenyl)aryl bromide **6a** and diethyl-1,2-hydrazine dicarboxylate **7** (Table 1). Dihalide **6a** was synthesized as reported[15] using simple Wittig chemistry, in good yield, and with high *Z*-selectivity. Based on literature precedent for aryl C–N bond formation with hydrazides,[18,19] we focused on a Cu^I diamine catalyst system. Treatment of dihalide **6a** with a catalyst generated from CuI and *N*,*N*′-dimethylethylenediamine (ligand **A**, DMEDA), using K_3PO_4 as the base in dioxane, produced the desired diethyldihydrocinnoline-1,2-dicarboxylate **8a** in moderate yield (Entry 1). Changing the base to Cs_2CO_3, and then K_2CO_3 increased the yield to 95% (Entries 2–3). When the strong base NaO*t*Bu was employed, only alkyne **6ab** was isolated as a reaction product (Entry 4). Other types of known Cu ligands were explored, however all were inferior to diamine **A** (Entries 5–6). Changing the copper source away from CuI also resulted in slightly reduced yields (Entries 7–8). Finally, a metal:ligand ratio of 1:2 with 10 mol% Cu^I loading was optimal; changing the ratio to 1:1 (Entry 9) and reducing the loading to 5 mol% (Entry 10) resulted in lower yields of 79% and 61%, respectively.

With the conditions optimized, we sought to explore the scope of this new process and a variety of diethyldihydrocinnoline-1,2-dicarboxylate derivatives **8** were prepared (Table 2). Electron-rich (**8b–f**), neutral (**8g–h**) and electron-poor (**8i–n**) arene cores were all readily incorporated. Although the majority of substrates featured an alkenyl bromide/aryl bromide combination of activating groups, it was also possible to employ aryl chloride units, as used in the preparation of dihydrocinnolines **8d**, **8e**, and **8g**. The ability to tolerate the incorporation of additional halogen substituents, useful for further functionalization, is also noteworthy (**8i–m**). Inclusion of additional alkene-substituents in the substrates was also possible, leading to C3-substituted dihydrocinnoline products (**8o–r**). A number of heterocycle-based substrates could be used, leading to the formation of aza derivative **8s**, thiophene derivative **8t**, and benzothiophene derivative **8u**. Finally, it should be noted that the *E*-isomers of the alkenyl bromide precusors **6** do not produce dihydrocinnoline products under the present reaction conditions, and lead instead to the formation of noncyclized byproducts. This is generally not an issue as the majority of substrates were obtained with $>10{:}1$ $Z{:}E$ selectivity. However, for selected substrates, lower $Z{:}E$ ratios resulted in reduced yields of dihydrocinnoline products (**8h**, **8t**, and **8u**, for example).

The range of dihydrocinnolines shown in Table 2 illustrates the variety of type and position of substituents that can

be introduced using this synthesis. In particular, we have shown that a Cl-substituent can be incorporated at each position of the benzo core. We have also prepared derivatives featuring a substituent at each position of the heterocycle, except C4. The difficulty in making C4-substituted products results from the use of Wittig chemistry for the preparation of the alkenyl bromide substrates **6**.[20] However, the inherent reactivity of diethyldihydrocinnoline dicarboxylates **8** can be used to produce C4 substituents in an efficient manner. For example, formylation of dihydrocinnoline **8g** using classic Vilsmeier–Haack conditions led exclusively to 4-formyl derivative **9**, and chlorination using NCS provided 4-chloro derivative **10**, both in good yields (Scheme 3). Capitalizing on

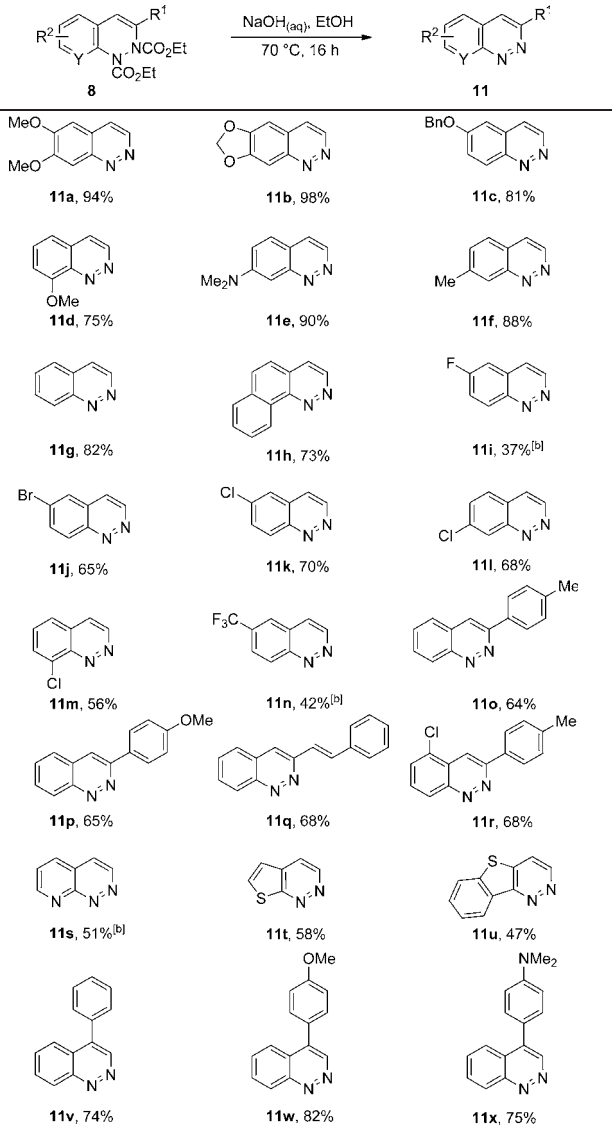


Scheme 3. Dihydrocinnoline functionalization and elaboration using a Suzuki coupling. NCS = *N*-chlorosuccinimide, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

the introduction of a Cl substituent, Suzuki conditions were developed utilizing Buchwald's electron-rich biaryl phosphine ligand, XPhos,[21] which allowed 4-aryl dihydrocinnolines **8v**–**x** to be prepared in excellent yields.

Next, our focus turned to the crucial transformation of the dihydrocinnoline derivatives **8** into their aromatic cinnoline counterparts. We found that a simple system of aqueous sodium hydroxide in ethanol left open to air led to the formation of cinnolines **11**, in generally good yields (Table 3). Cinnolines with strongly electron-donating substituents were readily prepared, presumably because of their increased propensity for oxidation. For example, cinnolines **11a**, **11b**, and **11e** were obtained in yields of 94%, 98%, and 90%, respectively. Less electron-rich substrates were transformed with lower efficiency, but still in generally good yields. Slightly modified conditions were required for the F containing cinnoline **11i** and for the strongly electron-deficient products (for example, **11n**). Under the standard conditions **11i** was observed to undergo an S_NAr reaction to yield the corresponding ethoxy-substituted product, and attempts to form **11n** resulted in decomposition. However, simply stirring the reactions at room temperature (as opposed to 70 °C) for an extended period of time (36 h) allowed formation of the desired cinnolines, albeit with reduced yields. The heterocycle-derived examples were also transformed into the corresponding aromatic systems, delivering the unusual aza cinnoline analogue **11s**,[22] and the novel thiophene-containing analogues **11t** and **11u**.[23]

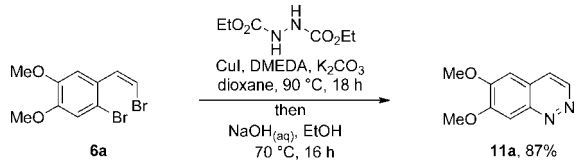
Table 3: NaOH mediated conversion of dihydrocinnoline derivatives **8** into cinnolines **11**.[a]



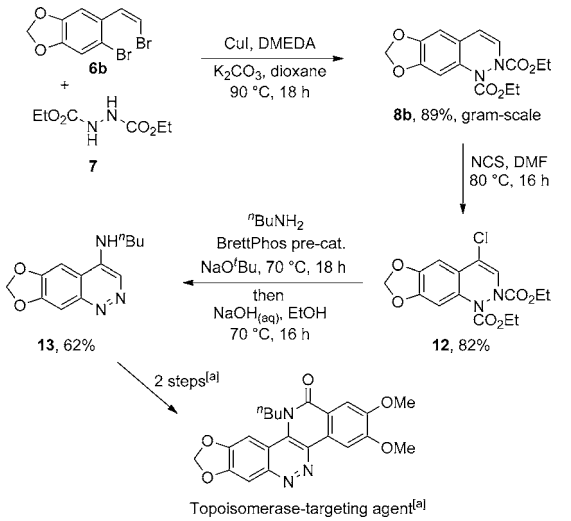
[a] Reaction conditions: diethyldihydrocinnoline-1,2-dicarboxylates (**8**, 1.0 equiv), 5 M $NaOH_{(aq)}$ (5.0 equiv), ethanol, 70 °C, 16 h. Yields of isolated product. [b] Left at room temperature for 36 h.

The cinnoline-forming conditions could also be performed as a "one-pot" process, without isolation of the intermediate dihydrocinnoline derivatives. Instead, the crude reaction mixture from the Cu-catalyzed transformation was simply filtered through Celite, concentrated under vacuum, and subjected directly to the cinnoline-forming conditions. As such, we prepared cinnoline **11a** on a gram scale in 87% yield (Scheme 4).

Finally, to fully demonstrate the utility of our cinnoline synthesis, we have prepared a medicinally important cinnoline derivative. Cinnoline **13** is an intermediate in the synthesis of a series of cinnoline-based Topoisomerase-targeting agents[7] (Scheme 5). Its previous synthesis relied on diazotization chemistry; however, we predicted that our direct annulation route would eliminate the need for a diazo-



Scheme 4. Gram scale "one-pot" formation of cinnoline **11a**.



Scheme 5. Synthesis of the pharmaceutically relevant cinnoline **13**, an intermediate in the synthesis of a Topoisomerase-targeting agent. BrettPhos = 2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl [a] See ref. [7].

nium intermediate. Dihydrocinnoline **8b** was synthesized on a gram scale in 89% yield, and then by using only a slight excess of NCS (1.05 eq) converted to chlorinated derivative **12** in high yield. Chloride **12** was then transformed into the key cinnoline target **13** by way of a two-step one-pot synthesis consisting of Pd-catalyzed amination followed by in situ deprotection and aromatization using NaOH. Chloride derivative **12** proved to be a challenging substrate for the desired amination reaction, and the use of Buchwald's BrettPhos ligand,[24] employed as a "pre-catalyst" complex,[25] was needed to achieve an efficient transformation. Conversion of amino cinnoline **13** into the target molecule is achieved in two known steps.[7]

In summary, we have reported a novel, general, and easy to perform two-step route to an under-used class of heterocyclic compounds, the cinnolines. Our method represents a departure from classical cinnoline-forming routes which are dominated by diazotization chemistry. Key features of our method include the use of readily available starting materials and catalysts, and the ability to introduce functionality at each position of the cinnoline ring. The dihydrocinnoline derivatives formed during our synthesis are also valuable intermediates, amenable to further functionalization. We have also demonstrated that the two-step route can be performed using a one-pot synthesis, and also applied this procedure to the synthesis of a medicinally relevant cinnoline derivative. Given the ease-of-use, efficiency and flexibility of this method, we anticipate that cinnolines will no longer be under represented in the literature.

Received: February 24, 2012
Revised: March 21, 2012
Published online: April 26, 2012

Keywords: annulation · cinnolines · copper catalysis · heterocycles · tandem processes

[1] a) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534.

[2] a) J. E. R. Sadig, M. C. Willis, *Synthesis* **2011**, 1–22; b) Y. Liu, J.-P. Wan, *Org. Biomol. Chem.* **2011**, *9*, 6873; c) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Biomol. Chem.* **2011**, *9*, 641; d) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; e) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127.

[3] a) W. Lewgowd, A. Stanczak, *Arch. Pharm.* **2007**, *340*, 65; b) Y. N. Yu, S. K. Singh, A. Liu, T. K. Li, L. F. Liu, E. J. LaVoie, *Bioorg. Med. Chem.* **2003**, *11*, 1475; c) A. L. Ruchelman, S. K. Singh, A. Ray, X. H. Wu, J. M. Yang, N. Zhou, A. Liu, L. F. Liu, E. J. LaVoie, *Bioorg. Med. Chem.* **2004**, *12*, 795; d) D. A. Scott, L. A. Dakin, D. J. Del Valle, R. B. Diebold, L. Drew, T. W. Gero, C. A. Ogoe, C. A. Omer, G. Repik, K. Thakur, Q. Ye, X. Zheng, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1382.

[4] a) P. Barraja, P. Diana, A. Lauria, A. Passannanti, A. M. Almerico, C. Minnei, S. Longu, D. Congiu, C. Musiu, P. La Colla, *Bioorg. Med. Chem.* **1999**, *7*, 1591; b) E. Gavini, C. Juliano, A. Mule, G. Pirisino, G. Murineddu, G. A. Pinna, *Arch. Pharm.* **2000**, *333*, 341; c) C. K. Ryu, J. Y. Lee, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1850.

[5] C. Lunniss, C. Eldred, N. Aston, A. Craven, K. Gohil, B. Judkins, S. Keeling, L. Ranshaw, E. Robinson, T. Shipley, N. Trivedi, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 137.

[6] a) T. Mitsumori, M. Bendikov, J. Sedo, F. Wudl, *Chem. Mater.* **2003**, *15*, 3759; b) V. G. Chapoulaud, N. Plé, A. Turck, G. Quéguiner, *Tetrahedron* **2000**, *56*, 5499; c) H. Tsuji, Y. Yokoi, Y. Sato, H. Tanaka, E. Nakamura, *Chem. Asian J.* **2011**, *6*, 2005.

[7] A. L. Ruchelman, S. K. Singh, X. H. Wu, A. Ray, J. M. Yang, T. K. Li, A. Liu, L. F. Liu, E. J. LaVoie, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3333.

[8] J. C. E. Simpson, *The Chemistry of Heterocyclic Compounds*, *Condensed Pyridazine and Pyrazine Rings*, *Cinnolines*, *Phthalazines and Quinoxalines*, *Vol. 5*, Wiley, New York, **1953**.

[9] a) V. von Richter, *Chem. Ber.* **1883**, *16*, 677; b) For the use of triazenes to access related intermediates, see: D. B. Kimball, A. G. Hayes, M. M. Haley, *Org. Lett.* **2000**, *2*, 3825.

[10] a) K. W. Woods, J. P. Fischer, A. Claiborne, T. Li, S. A. Thomas, G.-D. Zhu, R. B. Diebold, X. Liu, Y. Shi, V. Klinghofer, E. K. Han, R. Guan, S. R. Magnone, E. F. Johnson, J. J. Bouska, A. M. Olson, R. de Jong, T. Oltersdorf, Y. Luo, S. H. Rosenberg, V. L. Giranda, Q. Li, *Bioorg. Med. Chem.* **2006**, *14*, 6832; b) K. Schofield, T. Swain, *J. Chem. Soc.* **1950**, 392.

[11] a) H. E. Baumgarten, C. H. Anderson, *J. Am. Chem. Soc.* **1958**, *80*, 1981; b) C. B. Kanner, U. K. Pandit, *Tetrahedron* **1981**, *37*, 3513; c) M. S. Shvartsberg, I. D. Ivanchikova, *Tetrahedron Lett.* **2000**, *41*, 771; d) N. A. Al-Awadi, M. H. Elnagdi, Y. Ibrahim, K. Kaul, A. Kumar, *Tetrahedron* **2001**, *57*, 1609; e) M. A. M. Gomaa, *Tetrahedron Lett.* **2003**, *44*, 3493; f) A. S. Kiselyov, *Tetrahedron Lett.* **1995**, *36*, 1383; g) A. S. Kiselyov, C. Dominguez, *Tetrahedron Lett.* **1999**, *40*, 5111.

[12] a) E. J. Alford, K. Schofield, *J. Chem. Soc.* **1952**, 2102; b) for a Au^{I}-catalyzed approach to dihydrocinnolines, see: I. D. Jurberg, F. Gagosz, *J. Organomet. Chem.* **2011**, *696*, 37.

[13] a) D. Chen, C. Yang, Y. Xie, J. Ding, *Heterocycles* **2009**, *77*, 273; b) C. Alhambra, C. Becker, T. Blake, A. Chang, J. R. Damewood Jr., T. Daniels, B. T. Dembofsky, D. A. Gurley, J. E. Hall, K. J. Herzog, C. L. Horchler, C. J. Ohnmacht, R. J. Schmiesing, A. Dudley, M. D. Ribadeneira, K. S. Knappenberger, C. Maciag, M. M. Stein, M. Chopra, X. F. Liu, E. P. Christian, J. L. Arriza, M. Chapdelaine, *Bioorg. Med. Chem.* **2011**, *19*, 2927.

[14] M. Alajarin, B. Bonillo, M. Marin-Luna, A. Vidal, R.-A. Orenes, *J. Org. Chem.* **2009**, *74*, 3558.

[15] a) M. C. Willis, G. N. Brace, T. J. K. Findlay, I. P. Holmes, *Adv. Synth. Catal.* **2006**, *348*, 851; b) L. C. Henderson, M. J. Lindon, M. C. Willis, *Tetrahedron* **2010**, *66*, 6632; c) R. C. Hodgkinson, J. Schulz, M. C. Willis, *Tetrahedron* **2009**, *65*, 8940; d) For the use of a related alkenyl triflate substrate, see: M. C. Willis, G. N. Brace, I. P. Holmes, *Angew. Chem.* **2005**, *117*, 407; *Angew. Chem. Int. Ed.* **2005**, *44*, 403.

[16] A. C. Tadd, A. Matsuno, M. R. Fielding, M. C. Willis, *Org. Lett.* **2009**, *11*, 583.

[17] A. C. Tadd, M. R. Fielding, M. C. Willis, *Tetrahedron Lett.* **2007**, *48*, 7578.

[18] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13; b) A. Klapars, J. C. Antilla, X. H. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727; c) M. Wolter, A. Klapars, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803; d) R. Martín, M. R. Rivero, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 7237; *Angew. Chem. Int. Ed.* **2006**, *45*, 7079; e) M. R. Rivero, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 973.

[19] As far as we are aware, there are no reported examples of sequential Pd- or Cu-catalyzed *N*,*N*′-diarylation(alkenylation) of hydrazides leading to heterocycle synthesis.

[20] Introducing C4 substituents directly would require the Wittig reactions to be performed on the corresponding ketone substrates; these reactions are generally low yielding and poorly selective.

[21] R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

[22] C. M. Atkinson, B. N. Biddle, *J. Chem. Soc. C* **1966**, 2053.

[23] a) S. W. Schneller, P. N. Skancke, *Heterocycles* **1976**, *4*, 35; b) W. R. Pitt, D. M. Parry, B. D. Perry, C. R. Groom, *J. Med. Chem.* **2009**, *52*, 2952.

[24] B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552.

[25] D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27.