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# Diphosphine-Catalyzed Mixed Double-Michael Reaction: A Unified Synthesis of Indolines, Dihydropyrrolopyridines, Benzimidazolines, Tetrahydroquinolines, Tetrahydroisoquinolines, Dihydrobenzo-1,4-oxazines, and Dihydrobenzo-3,1-oxazines

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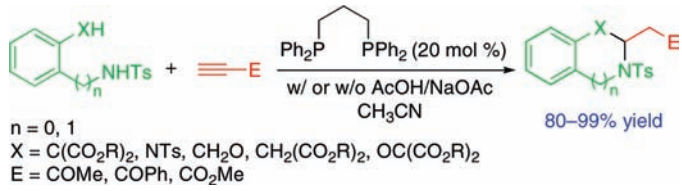
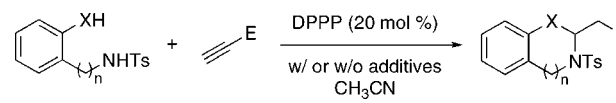
## ABSTRACT




**Seven different types of benzannulated *N*-heterocycles—indolines, dihydropyrrolopyridines, benzimidazolines, dihydrobenzo-3,1-oxazines, benzomorpholines, tetrahydroquinolines, and tetrahydroisoquinolines—can be obtained from simple dinucleophiles and electron-deficient acetylenes in one synthetic step. This powerful methodology was made possible through the use of diphenylphosphinopropane (DPPP) as the catalyst, with acetic acid and sodium acetate used as additives in some cases. The benzannulated *N*-heterocycles were isolated in excellent yields under mild metal-free conditions; they were purified without the need for aqueous workups.**

Functionalized saturated benzannulated *N*-heterocycles (e.g., indoline, dihydropyrrolopyridine, benzimidazoline, tetrahydroquinoline, tetrahydroisoquinoline, dihydrobenzo-1,4-oxazine, dihydrobenzo-3,1-oxazine) have been of interest to chemists for over a century because of their seemingly ubiquitous presence in natural products[1] and pharmaceutical drugs.[2] Not surprisingly, several useful strategies are available for the synthesis of these heterocycles, with the majority of them typically generating one or two of the compounds mentioned above.[3] Based on our recent finding of a diphosphine-catalyzed mixed double-Michael reaction that proceeds through a [4 + 1] annulation, in this paper we report a unified protocol for the synthesis of the title heterocycles under robust metal-free reaction conditions (Scheme 1).[4] Our

**Scheme 1.** Formation of Benzannulated Heterocycles




(1) Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455.

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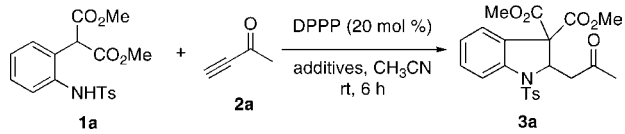
**Table 1.** Evaluation of Conditions for the Formation of Indoline **3a**[a]




| entry | acid | p$K_a$[b] | conjugate base | yield (%)[c] with acid | yield (%)[c] with acid/base |
|---|---|---|---|---|---|
| 1 | none | | none | 79 | N/D |
| 2 | $CF_3CO_2H$ | −0.25[d] | $CF_3CO_2Na$ | 0 | 0 |
| 3 | $H_3PO_4$ | 2.1[d] | N/A | 0 | N/D |
| 4 | 2,4-dinitrophenol | 5.1 | N/A | 0 | N/D |
| 5 | $CH_3CO_2H$ | 12.6 | $CH_3CO_2Na$ | 92 | 99 |
| 6 | bi(2-naphthol) | 16.2 | + *n*-BuLi | 81 | 94 |
| 7 | thiourea | 21.0 | + *n*-BuLi | 57 | 68 |
| 8 | $NaHCO_3$ | 10.2[d] | $Na_2CO_3$ | 80 | 87 |
| 9 | $CF_3CH_2OH$ | 23.5 | $CF_3CH_2ONa$ | 91 | 93 |
| 10 | urea | 26.9 | + *n*-BuLi | 82 | 85 |
| 11 | $H_2O$ | 31.4 | NaOH | 67 | 75 |

[a] All reactions were performed using 1.0 mmol of **1a**, 1.1 mmol of acetylacetylene (**2a**), 20 mol % of DPPP, and 0.50 mmol of the additive(s). [b] p$K_a$ in DMSO. [c] Isolated yield. [d] p$K_a$ in $H_2O$.

approach is highly modular and particularly well suited for the preparation of substituted saturated benzannulated *N*-heterocycles. The requisite dinucleophiles are readily assembled from commercially available starting materials.[5] Given the common occurrence of the title heterocycles in a large number of bioactive molecules, this methodology should provide new avenues toward the preparation of compounds relevant to the development of human medicines.

As a test case for the construction of aniline-containing benzannulated heterocycles, we subjected the nucleophile **1a** and acetylacetylene (**2a**) to our previously reported mixed double-Michael reaction conditions: i.e., 20 mol % of diphenylphosphinopropane (DPPP) in $CH_3CN$ (Table 1, entry 1). The desired indoline **3a** was obtained in 79% yield.[6] Although this yield is acceptable synthetically, the reaction efficiency was markedly poorer than that for pyrrolidine formation from a corresponding aliphatic amine-derived nucleophile (91% vs 79%). To improve the reaction efficiency, we tested Brønsted acid additives that are known to be compatible with nucleophilic phosphine catalysis.[7] To our delight, addition of 50 mol % of AcOH provided a reaction efficiency comparable with that of aliphatic amine-derived nucleophiles (entry 5; 92% yield).[8] The combination of a Brønsted acid and its conjugate base performed even better; we obtained indoline **3a** in 99% yield in the presence of AcOH and NaOAc (50 mol % each).[9] Indeed, for several common Brønsted acid additives, pairs of acids and bases, rather than the acids or bases alone, consistently provided higher product yields (entries 5−11).[10] Although there was no clear correlation between the p$K_a$ of the Brønsted acid and the reaction efficiency, additives of low p$K_a$ completely shut down the reaction, presumably through quenching of the reactive zwitterionic intermediates (entries 2−4).[11] Notably, one inorganic acid/base pair ($NaHCO_3/CO_3^{2-}$) improved the reaction yield by 8%, whereas another ($H_2O$/NaOH) did not (entries 8 and 11).[12] The added acid/base pair presumably facilitated the proton transfer steps involved in the double-Michael process.

The combination of DPPP catalyst and AcOH/NaOAc

(2) The Chemical Abstracts Service (CAS) database provided the following numbers of references for each heterocycle: indoline, 3374 patents, 102 reviews; benzimidazoline, 1085 patents, 19 reviews; tetrahydroquinoline, 2020 patents, 38 reviews; tetrahydroisoquinoline, 2165 patents, 361 reviews; dihydrobenzoxazines, 928 patents, 25 reviews.

(3) For reviews on their synthesis, see: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. (b) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449. (c) Ilas, J.; Anderluh, P. S.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325. (d) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. For selected examples, see: (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (f) Liu, X.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2367.

(4) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928.

(5) See the Supporting Information for the preparation of the starting materials.

(6) With 20 mol % of the monodentate tertiary phosphines $PPh_3$ and $PEtPh_2$, we obtained **3a** in 18 and 23% yields, respectively.

(7) For selected examples, see: (a) Takashina, N.; Price, C. C. *J. Am. Chem. Soc.* **1962**, *84*, 489. (b) Oda, R.; Kawabata, T.; Tanimoto, S. *Tetrahedron Lett.* **1964**, *5*, 1653. (c) McClure, J. D. *J. Org. Chem.* **1970**, *35*, 3045. (d) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659. (e) Thalji, R. K.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 16778. (f) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (g) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3613.

(8) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933.

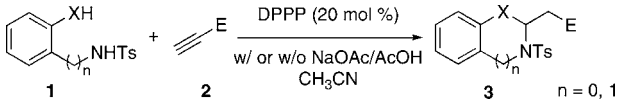
(9) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

(10) See the Supporting Information for a list of all of the additives tested.

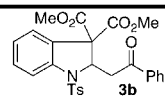
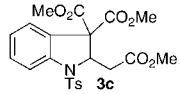
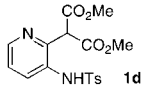
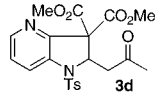
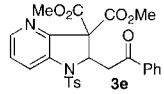
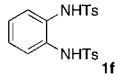
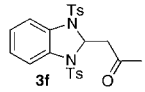
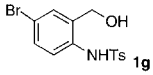
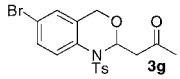
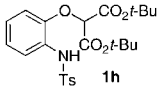
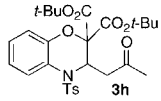
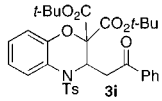
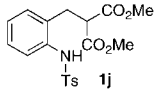
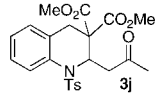
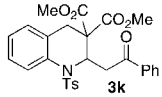
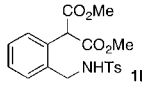
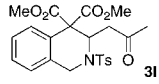
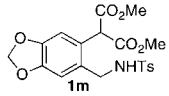
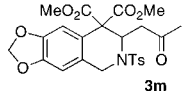
(11) Virieux, D.; Guillouzic, A.-F.; Cristau, H.-J. *Tetrahedron* **2006**, *62*, 3710.

(12) For Brønsted acid/phosphine bifunctional catalysis, see: (a) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (b) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (c) Fang, Y.-Q.; Jacobsen, E. *J. Am. Chem. Soc.* **2008**, *130*, 5660. (d) Meng, X.; Huang, Y.; Chen, R. *Org. Lett.* **2009**, *11*, 3498, and references cited therein.

**Table 2.** Syntheses of Benzannulated N-Heterocycles[a]




1 2 3

| entry | nucleophile | product | yield (%)[b] |
|---|---|---|---|
| 1 | **1a** |  **3b** | 92 |
| 2 | **1a** |  **3c** | 87 |
| 3[c] |  **1d** |  **3d** | 94 |
| 4[c] | **1d** |  **3e** | 96 |
| 5[c] |  **1f** |  **3f** | 81 |
| 6[c] |  **1g** |  **3g** | 88 |
| 7[d] |  **1h** |  **3h** | 81 |
| 8[d] | **1h** |  **3i** | 80 |
| 9[d] |  **1j** |  **3j** | 91 |
| 10[d] | **1j** |  **3k** | 92 |
| 11[e] |  **1l** |  **3l** | 83 |
| 12[e] |  **1m** |  **3m** | 82 |

[a] Performed using 1.0 mmol of the nucleophile, 1.1 mmol of the acetylene, 20 mol % of DPPP, and 0.50 mmol of AcOH and NaOAc in $CH_3CN$ at rt, unless otherwise noted. [b] Isolated yields after chromatographic purification. [c] Reactions were performed under reflux. [d] Reactions were run in the absence of AcOH/NaOAc in $CH_3CN$ under reflux. [e] In the absence of AcOH/NaOAc in $CH_3CN$ at rt.

additives provided a variety of aniline-containing heterocycles efficiently (Table 2).[13] With the phenylmalonate nucleophile **1a**, both benzoylacetylene and methyl propiolate were suitable Michael acceptors (entries 1 and 2). A variety of substituents on the benzene ring (cf. entries 6 and 12) as well as heteroaromatic rings were compatible with the reaction. For instance, the pyridylmalonate **1d** provided the dihydropyrrolopyridines **3d** and **3e** in excellent yields at elevated temperature (entries 3 and 4). The 1,2-benzenediamine-derived nucleophile **1f** also underwent the double-Michael reaction to provide the benzimidazoline **3f** (entry 5). This result is in stark contrast with Lu's report of the tandem umpolung addition/Michael reactions of 1,2-di(*p*-toluenesulfonamido)ethane onto acetylenes.[14] Benzimidazolines are not only important biologically—they are used as sources of organic hydrides and hydrogen storage materials.[15]

Next, we extended this chemistry to 1,5-dinucleophiles for the synthesis of six-membered ring-fused benzannulated heterocycles via [5 + 1] annulation. The benzyl alcohol **1g** reacted well under the optimized reaction conditions, providing the dihydrobenzo-3,1-oxazine **3g** in 88% isolated yield (entry 6). A notable extension of this methodology is represented by the annulations of the related nitrogen−carbon dinucleophile **1h** to give the benzomorpholines **3h** and **3i** (entries 7 and 8), which slowly decomposed in the presence of AcOH and NaOAc in refluxing $CH_3CN$; we found, however, that catalytic DPPP alone provided slightly better product yields.[16] Dihydrobenzo-1,4- and -3,1-oxazines have long been recognized for their wide range of medicinal activities (e.g., antibacterial, neuroprotectant, cardiovascular, antitumor).[17]

We further extended this [5 + 1] annulation to the synthesis of tetrahydroquinolines and tetrahydroisoquinolines (Table 2, entries 9−12). The benzylmalonate **1j**, when mixed with electron-deficient acetylenes and catalytic DPPP, generated the tetrahydroquinolines **3j** and **3k** in excellent yields (entries 9 and 10). The tetrahydroisoquinolines **3l** and **3m** were formed from the corresponding benzylamine-derived pronucleophiles **1l** and **1m** (entries 11 and 12). Tetrahydroquinolines and -isoquinolines are present in many natural products and exhibit a wide range of pharmacological activities.[18]

To summarize, seven different types of bicyclic heterocycles—indoline, dihydropyrrolopyridine, benzimidazoline, dihydrobenzo-3,1-oxazine, dihydrobenzo-1,4-oxazine, tetrahydroquinoline, and tetrahydroisoquinoline—can be synthesized in one step, in excellent yields, from simple dinucleophiles and electron-deficient acetylenes. The Michael reaction is one of the most important fundamental organic reactions; our study highlights the power of the Michael reaction when applied to the right combination of starting materials under suitable reaction conditions. This versatile catalysis was mediated by DPPP with, in some cases, AcOH/NaOAc additives. This DPPP-catalyzed mixed double-

(13) The structures of **3a**,**f**−**h**,**j**,**m** were confirmed through X-ray crystallographic analysis. See the Supporting Information for details.

(14) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677.

(15) (a) Smith, J. G.; Ho, I. *Tetrahedron Lett.* **1971**, *38*, 3541. (b) Prakash, G. K. S.; Mathew, T.; Panja, C.; Vaghoo, H.; Venkataraman, K.; Olah, G. A. *Org. Lett.* **2007**, *9*, 179, and references therein.

(16) See the Supporting Information for details.

(17) (a) Gromachevskaya, E. V.; Kvitkovskii, F. V.; Kosulina, T. P.; Kul'nevich, V. G. *Chem. Heterocycl. Compd.* **2003**, *39*, 137. (b) Liu, Z.; Chen, Y. *Tetrahedron Lett.* **2009**, *50*, 3790, and references therein.

(18) (a) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A., Ed.; Pergamon Press: Oxford, 1996; Vol. 5, Chapter 5, pp 245−300. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

Michael reaction should be further expandable to the assembly of other heterocycles—one goal for our future endeavors.

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**Supporting Information Available:** Representative experimental procedures and spectral data for all new compounds. Crystallographic data for **3a**,**f**−**h**,**j**,**m** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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