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Nickel-catalyzed alkyne annulation by anilines: versatile indole synthesis by C–H/N–H functionalization<sup>†</sup>

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Versatile nickel catalysts enabled the step-economical synthesis of decorated indoles through alkyne annulations with anilines bearing removable directing groups. The C–H/N–H activation strategy efficiently occurred in the absence of any metal oxidants and with excellent selectivities.

Indoles are key structural motifs in bioorganic chemistry, drug discovery and medicinal chemistry.<sup>1,2</sup> Therefore, there is a continuous strong demand for chemo- and site-selective syntheses of this heteroaromatic scaffold. While palladium-catalyzed C-C and C-N bond forming reactions have been particularly proven to be valuable for the preparation of indoles, these transformations largely relied on prefunctionalized starting materials.<sup>2</sup> Significantly more step-economical strategies are represented by methods that capitalize upon unactivated C-H bonds as latent functional groups.<sup>3</sup> As of yet, solely expensive second-row transition metal catalysts, such as rhodium, palladium, or ruthenium complexes,<sup>4</sup> have been utilized for indole syntheses by oxidative alkyne annulation through C-H/N-H bond functionalizations.<sup>5</sup> Furthermore, these methods relied on the use of copper(II) or silver(I) salts as the stoichiometric or cocatalytic oxidants. Recent notable progress in the use of naturally more abundant nickel<sup>6</sup> catalysts for C-H bond functionalizations<sup>7</sup> was accomplished by Chatani and coworkers with a versatile isoquinolone synthesis from arenes bearing electron-withdrawing amides.8 However, the atom-economical nature of this approach was compromised by the need for a specific, less atom-economical bidentate directing group. In consideration of the practical importance of modular indole syntheses, we became interested in developing unprecedented nickelcatalyzed alkyne annulations by electron-rich anilines, which we wish to report herein.

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Scheme 1 Environmentally-benign indole synthesis

Notable features of our strategy are not limited to (a) the use of easily removable, monodentate directing groups, (b) a high catalytic efficacy with challenging electron-rich anilines, and (c) in contrast to previous indole syntheses,<sup>4</sup> oxidative alkyne annulations devoid of copper(u) or silver(i) salts as the sacrificial oxidants (Scheme 1).

We commenced our studies by identifying the reaction conditions for the envisioned nickel-catalyzed indole synthesis with pyridyl-substituted aniline 1a (Table 1). Among a variety of ligands, bidentate dppf, in combination with Ni(cod)<sub>2</sub>, proved to be optimal (entries 1-9). We were pleased to find that stoichiometric amounts of copper(II) or silver(I) salts were not required as sacrificial oxidants-a notable advantage over previously developed protocols.<sup>4,9</sup> Interestingly, the formation of indole 3aa occurred most efficiently in the absence of solvents (entries 10-14), thereby further improving the environmentallybenign nature of our approach. Control experiments verified that the formation of indole 3aa was neither achieved in the absence of  $Ni(cod)_2$  nor without the dppf ligand (entries 15 and 16). Moreover, our studies revealed that representative palladium or cobalt complexes in lieu of the nickel(0) catalyst were ineffective (entries 17 and 18).

With an optimized catalytic system in hand, we explored its versatility in the oxidative annulation of alkyne 2a (Scheme 2). Given that the *N*-2-pyrimidyl group is easily removed from the indole nucleus, we focused our studies on the use of *N*-pyrimidyl-substituted anilines **1**. We were delighted to find that the challenging pyrimidyl-substituted substrate **1b** was converted with a comparably high efficacy compared to reactions with the more electron-rich aniline **1a**. The optimized

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Table 1 Optimization of the nickel-catalyzed oxidative annulation<sup>a</sup>

1a	.H Pr     N <sup>-</sup> H     -Py 2a	cat. [TM] cat. ligand solvent, 160 °C 20 h py = pyridine		Ph / Ph Py
Entry	[TM]	Ligand	Solvent	Yield (%)
1	Ni(cod) <sub>2</sub>	TMEDA	PhMe	_
2	$Ni(cod)_2$	Terpyridine	PhMe	_
3	$Ni(cod)_2$	$PPh_3^{b}$	PhMe	40
4	Ni(cod) <sub>2</sub>	dcype	PhMe	—
5	$Ni(cod)_2$	rac-BINAP	PhMe	21
6	Ni(cod) <sub>2</sub>	dppp	PhMe	30
7	$Ni(cod)_2$	DPEphos	PhMe	30
8	$Ni(cod)_2$	Xantphos	PhMe	43
9	Ni(cod) <sub>2</sub>	dppf	PhMe	48
10	$Ni(cod)_2^c$	dppf	PhMe	63
11	$Ni(cod)_2^c$	dppf	<i>m</i> -Xylene	45
12	$Ni(cod)_2^c$	dppf	o-Xylene	35
13	$Ni(cod)_2^c$	$PPh_3^{b}$	_	65
14	$Ni(cod)_2^c$	dppf	—	82
15		dppf	—	
16	$Ni(cod)_2^c$	_	PhMe	
17	$Pd_2(dba)_3^c$	dppf	PhMe	—
18	$\operatorname{Co}_2(\operatorname{CO})_8^c$	dppf	PhMe	_

<sup>a</sup> Reaction conditions: 1a (0. 50 mmol), 2a (1.5 mmol), [TM] (10 mol%), ligand (20 mol%), 160 °C, 20 h, isolated yields. <sup>b</sup> PPh<sub>3</sub> (40 mol%). <sup>c</sup> 2a (2.5 mmol).



nickel(0) catalyst proved to be widely applicable, and allowed for the use of functionalized as well as sterically hindered orthosubstituted anilines 1, thereby furnishing the desired indoles 3ba-3ia. It is particularly notable that reactive electrophilic functional groups, such as the chloro, acetyl or cyano substi-

for further derivatization of the thus obtained products 3ja-3la. Subsequently, we tested the scope of the nickel catalyst with a representative set of substituted alkynes 2 (Scheme 3). We observed that tolane derivatives 2b-2d featuring either electrondonating or electron-withdrawing groups were efficiently converted by the optimized nickel complex. However, the catalytic system was not restricted to tolanes. Indeed, dialkylalkyne 2e provided the desired product as well. Importantly, the C-H/N-H

tuents, were well tolerated, which should prove instrumental





Scheme 3 Catalyzed C-H/N-H bond functionalization with alkynes 2.





bond functionalization with the unsymmetrical alkyne 2f10 yielded the corresponding indole 3bf with an excellent regioselectivity.

For future practical applications it is important to note that the 2-pyrimidyl group was easily removed from indole 3ba to deliver the corresponding NH-free indole 4 (Scheme 4).

Considering the remarkable reactivity of the nickel(0) catalyst, we became interested in rationalizing its mode of action. To this end, we conducted intramolecular competition experiments with meta-substituted anilines 1m-o. Here, the site-selectivity of the C-H bond functionalization was largely governed by steric interactions, while a fluoro-substituent<sup>11</sup> led to significant amounts of product 30a" through C-H bond functionalization at the C-2 position (Scheme 5).

Furthermore, intermolecular competition experiments with differently substituted alkynes 2 highlighted arylacetylenes to be preferentially converted (Scheme 6a),<sup>12</sup> while electron-deficient arenes were found to be more reactive (Scheme 6b). These experimental



Scheme 5 Experiments with meta-substituted arenes 1m-o



2-pvm

2-`pym

 3ea: 32%
 3da: 23%

 Scheme 6
 Intermolecular competition experiments.



findings are in good agreement with a rate-determining migratory alkyne insertion.

Furthermore, we performed oxidative annulations with isotopically labeled substrate [D]<sub>5</sub>-**1b** (Scheme 7), revealing a considerable H/D exchange. Notably, scrambling with the free N-H functionality exclusively occurred at the *ortho*-positions of the arene. These results, thus, provide strong support for an initial reversible C–H/N–H bond activation event to be operative.

Based on our mechanistic studies we consequently propose the catalytic cycle to involve an initial reversible C–H/N–H bond activation of aniline **1**. Subsequent migratory insertion and reductive elimination furnish the desired indole **3** and regenerate the catalytically active nickel complex.

In summary, we have reported an unprecedented nickelcatalyzed oxidative alkyne annulation by electron-rich anilines with removable directing groups. The C–H/N–H bond functionalizations proceeded with excellent chemo-, regio- and siteselectivities in the absence of metal salts as oxidants, thereby furnishing substituted indoles with a broad scope. Experimental mechanistic studies provided support for reversible C–H/N–H bond activation, and are suggestive of a rate-limiting migratory alkyne insertion.

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