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Nickel-Catalyzed *trans*-Carboamination across Internal Alkynes to Access Multifunctionalized Indoles

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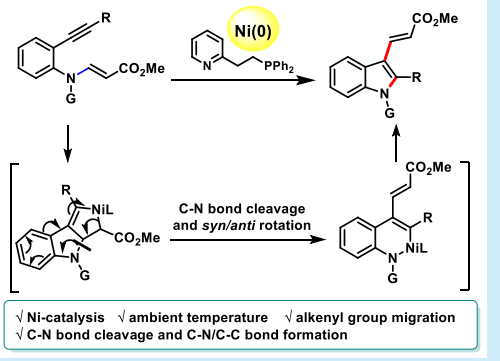
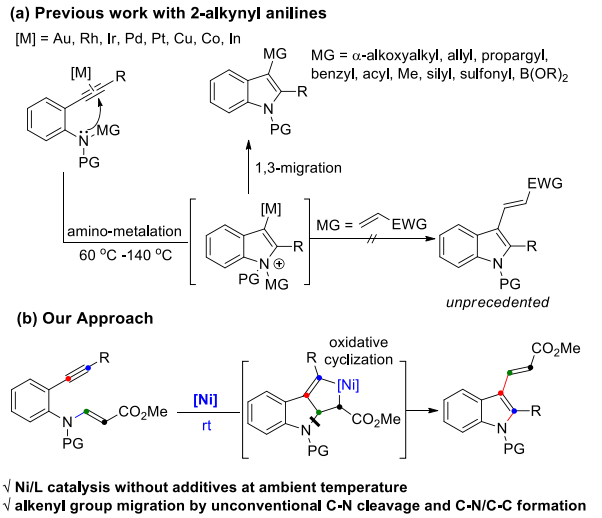
ABSTRACT: A Ni-catalyzed reaction was developed for the synthesis of multifunctionalized indoles. The reaction proceeded through oxidative cyclization of the Ni(0)/P^N complex with an enyne system, 2-alkynyl anilinoacrylate, to provide a nickelacycle intermediate. The *trans*-carboamination around the internal alkyne was achieved by *syn*/*anti*-rotation of the Ni-carbenoid intermediate formed by C−N bond cleavage of the nickelacycle, and 3-alkenylated indoles were formed by C−N bond-forming reductive elimination. Notably, the synthesized indoles could be successfully transformed to functionalized carbazoles.



Indoles are considered one of the most privileged structural motifs in drug development, particularly because of their compatibility with the human body. The compatibility stems from the fact that the indole moiety is present in an essential amino acid, tryptophan, and is also an important skeletal backbone of naturally occurring alkaloids and biologically active molecules.[1] Various electronic materials also contain the indole moiety.[2] Due to their physiological relevance and their scope in practical applications, various synthetic methodologies have been developed over the years to construct indole systems.[3] Transition-metal-catalyzed annulation of 2-alkynyl aniline derivatives has gained significant attention due to the ease of substrate synthesis and high atom economy of the process.[3−5] The transformations involve the formation of alkenyl−metal (Pd, Pt, Rh, Ir, Au, Cu, Co, In) complex intermediates that undergo either electrophilic trapping or 1,3-migration of a broad range of functional groups including methyl, allyl, benzyl, propargyl, α-alkoxyalkyl, acyl, silyl, sulfonyl, and $B(OR)_2$ groups to afford diverse indole structures (Scheme 1a). Despite the efficiency and broad applications of this reaction, it has certain drawbacks. This includes a limited substrate scope, wherein no alkenyl group migration occurs, and the requirement of a high temperature.[6]

To overcome these limitations, we envisioned an alternative Ni-catalyzed *trans*-carboamination approach. A suitable ligand for driving the alkenyl group migration was chosen to afford 3-alkenyl indoles at ambient temperature. We hypothesized that alkenyl group migration can be achieved by nickelacycle formation[7] with an enyne system, 2-alkynyl anilinoacrylate, followed by the C−N bond cleavage to give a Ni-carbenoid intermediate. Then, the key process, *trans*-carboamination around the alkyne, could be achieved by the *syn*/*anti*-rotation of the Ni-carbenoid intermediate,[8] followed by a new C−N bond-forming reductive elimination (Scheme 1b). This transformation would allow rapid access to multisubstituted indoles

Scheme 1. Metal-Catalyzed Cycloisomerization for Indole Synthesis



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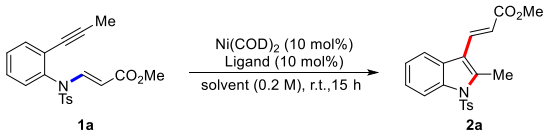
in an atom-economical manner at ambient temperature. Additionally, the substituent at the 2-position of the indoles could be easily varied by modifying the alkyne moiety in the substrate, allowing the rapid buildup of diversity.

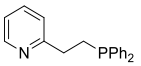
We commenced our investigation with tosylated methyl 2-propynyl anilinoacrylate **1a** as the model substrate, using $Ni(COD)_2$ as the catalyst. The reaction was conducted at ambient temperature in CH_3CN (Table 1). The desired indole

Table 1. Optimization of Reaction Conditions[a]



entry	ligand	solvent	yield (%)[b]
1	DPPF	CH_3CN	32
2	DPPP	CH_3CN	0
3	DPEPhos	CH_3CN	11
4	BINAP	CH_3CN	11
5	(*S*)-SEGPhos	CH_3CN	0
6	bpy	CH_3CN	10
7	^{t}Bubpy	CH_3CN	3
8	TerPy	CH_3CN	0
9	PCy_3	CH_3CN	95 (*E*/*Z* = 2.5/1)
10	$(p\text{-tolyl})_3P$	CH_3CN	85 (*E*/*Z* = 1.2/1)
11	PyPhos	CH_3CN	98
12	PyPhos	DCM	13
13	PyPhos	THF	19
14	PyPhos	dioxane	11
15	PyPhos	DMF	30
16	PyPhos	toluene	0
17	PyPhos	TFE	0
18	PyPhos	CH_3OH	trace
19[c]	PyPhos	CH_3CN	29
20[d]	PyPhos	CH_3CN	0
21		CH_3CN	0

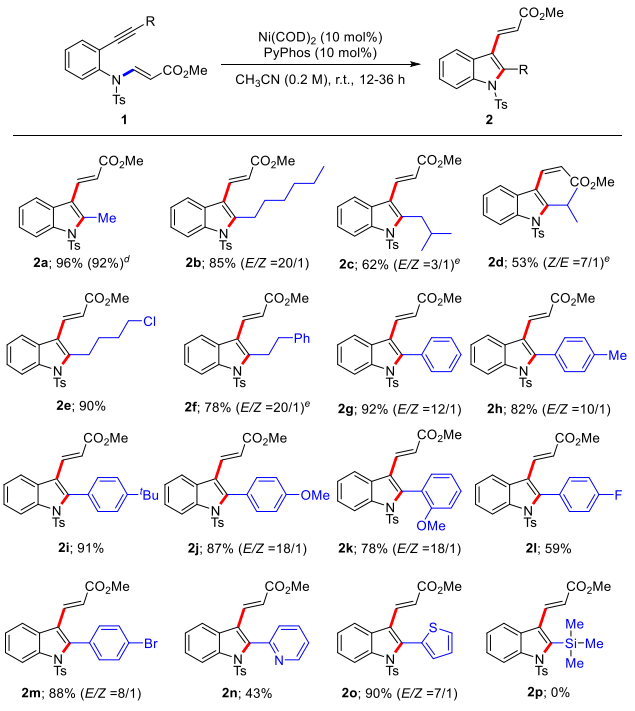
[a]Reaction conditions: **1a** (0.1 mmol). [b]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Reaction under air. [d]Reaction without $Ni(COD)_2$. DPPF {1,1′-ferrocenediyl-bis(diphenylphosphine)}, DPPP {1,3-bis(diphenylphosphino)propane}, DPEPhos {bis[(2-diphenylphosphino)phenyl]ether}, BINAP {(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)}, (*S*)-SEGPhos {(*S*)-(−)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole}, bpy {2,2′-bipyridine}, ^{t}Bubpy {4,4′-di-*tert*-butyl-2,2′-dipyridyl}, PCy_3 {tricyclohexylphosphine}, TerPy {2,2′:6′,2″-terpyridine}, $(p\text{-tolyl})_3P$ {tri(*p*-tolyl)phosphine}, PyPhos {2-[2-(diphenylphosphanyl)ethyl]pyridine}



2a with alkenyl substitution at the 3-position could be obtained with several types of ligands. The P^P-, N^N-, and N^N^N-type ligands were found to be less effective for the transformation (Table 1, entries 1−8).[9] A dramatic increase in reactivity was observed when monodentate phosphorus ligands were employed, although *E*/*Z* mixtures were obtained (Table 1, entries 9 and 10). Notably, the use of a P^N-type bidentate ligand, PyPhos,[10] which has not been explored much with Ni(0) complexes,[11] showed excellent reactivity, affording **2a** in 98% yield as only the *E*-isomer. This suggested that the reactivity could be tuned by carefully selecting the ligand (Table 1, entry 11). The choice of solvent was also critical for this reaction, as no other solvents employed could produce **2a** in significant yields (Table 1, entries 12−18). The presence of molecular oxygen lowered the reaction efficacy (Table 1, entry 19), whereas controlled experiments revealed that Ni and the ligand were essential for the reaction to proceed (Table 1, entries 20 and 21). The selective alkenyl group migration over the tosyl group migration is noteworthy.[4a]

With the optimized conditions in hand, various indole derivatives were synthesized to confirm the generality of this transformation. First, the substituent in the alkynyl moiety (R) was varied to obtain different substitution patterns at the 2-position (Scheme 2). Substrates with both aliphatic (**2a−2f**)

Scheme 2. Substrate Scope with Variations on Alkyne Moiety[a,b,c]



[a]Reaction conditions: **1** (0.3 mmol), under inert atmosphere. [b]Isolated yields are reported. [c]In some reactions, *E*/*Z* isomerization was observed during the reaction course, and the *E*/*Z* ratio is based on an average of at least two runs. [d]3 mmol scale. [e]The reaction was conducted at 80 °C.

and (hetero)aromatic (**2g−2o**) substituents at this position underwent *trans*-carboamination to provide the corresponding indole derivatives, demonstrating the generality of this reaction. Substrates with aromatic R substituents containing an electron-withdrawing group required a longer reaction time (**2h−2k** vs **2l**, **2m**). Functional groups such as benzylic C−H (**2h**) and aryl halides (**2l**, **2m**) remained intact during this transformation, suggesting that the reaction proceeded under mild conditions. It is noteworthy that heteroaryl moieties such as pyridine (**2n**) and thiophene (**2o**) can be easily substituted at the 2-position of the indoles. Such compounds are not only potential bidentate ligands but also important from a medicinal point of view. The silyl variant (**2p**) did not work for the transformation.[6b] The scale-up of **2a** from **1a** at the 3 mmol scale was straightforward despite the slower conversion.

Next, the substituent on the aniline moiety was varied (Scheme 3). Regardless of the electron density of the

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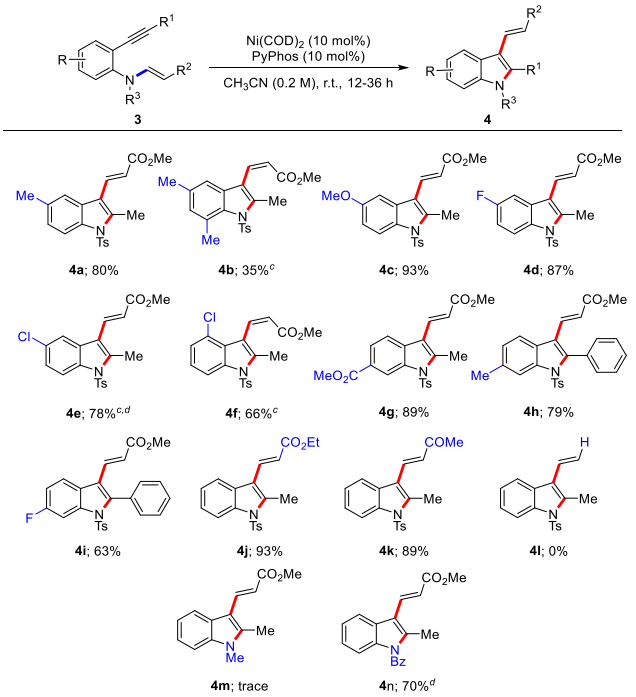
Scheme 3. Substrate Scope[a,b]

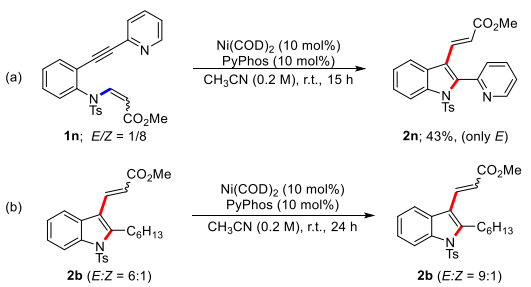


[a]Reaction conditions: **1** (0.3 mmol), under inert atmosphere. [b]Isolated yields are reported. [c]Only *Z*-isomer of the starting material reacted to give *Z*-isomer of the product. [d]The reaction was conducted at 80 °C.

substituents, reactions proceeded efficiently to give the corresponding indole derivatives in good to excellent yields (**4a**−**4i**). Interestingly, in the case of 3- or 6-substituted aniline substrates, only *Z*-isomers reacted to give the corresponding indoles with *Z*-selectivity (**4b**, **4f**). The modification of the methylester moiety to ethylester (**4j**) and ketone (**4k**) analogues was not problematic to give the corresponding products, whereas the terminal enamine (**4l**) was not a suitable substrate. N-Substitution with benzoyl instead of the tosyl group also led to product formation (**4n**) despite longer reaction time and higher temperature. However, the *N*-Me derivative (**4m**) did not work for the transformation well.

Some reactions provided *E*/*Z* mixtures of the product dependent on the substituent pattern. The control experiments showed that *E*/*Z* isomerization occurred over time during the reaction course (Scheme 4). The reaction with *E*/*Z* mixtures of substrate **1n** produced only the corresponding *E* product under standard conditions (Scheme 4a). The *E*/*Z* ratio was changed when isolated *E*/*Z* mixtures of **2b** was resubjected to the

Scheme 4. Control Experiment to Investigate *E*/*Z* Selectivity

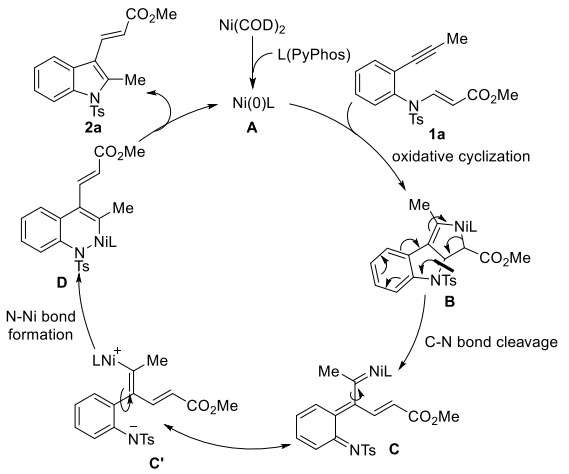


reaction conditions (Scheme 4b). *E*/*Z* isomerization might occur under the Ni-catalyzed conditions through coordination with the acrylate system.[8,12,13] The change of the *E*/*Z* ratio during the reaction course was also observed in the reaction of **1d**, where unpredictably the *E*-isomer was changed to *Z*, resulting in the formation of (*Z*)-**2d** as the major product (Scheme S1). It is likely that the steric hindrance of the isopropyl substituent affected the *Z*-selectivity. In the same context, only *Z*-isomers of **3b** and **3f** having substitution at the 3- or 6-position reacted to yield (*Z*)-**4b** and (*Z*)-**4f**, respectively (Scheme 3).

Further, a cross-over experiment of **3g** and **3j** did not show crossing-over phenomena, supporting the efficient intramolecular process (Scheme S2).

Based on the above observations, a plausible mechanism for the reaction of **1a** is proposed (Scheme 5). The Ni(0) complex

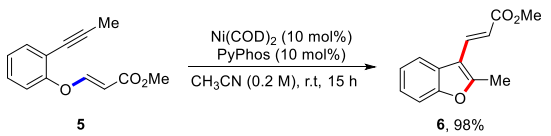
Scheme 5. Proposed Mechanism



A formed by the chelation between Ni(0) and PyPhos undergoes an oxidative cyclization with the alkyne and alkene moiety of 2-propynyl anilinoacrylate **1a** to give nickelacycle intermediate **B**. Then **B** undergoes C−N bond cleavage to generate Ni-carbenoid intermediate **C**. The *syn*/*anti* rotation of **C** to give a zwitterionic Ni intermediate **C′**,[8] followed by N−Ni coordination, generates six-membered intermediate **D**. Finally, **D** undergoes reductive elimination to give the corresponding indole **2a** with 3-alkenyl substitution.

The developed method could be extended to the benzofuran synthesis, showing the generality of the process (Scheme 6). An O analogue **5** was converted to the corresponding benzofuran **6** in 98% yield.[14]

Scheme 6. Benzofuran Synthesis



Next, the synthetic utility of this reaction was successfully verified by its application for the synthesis of functionalized carbazole (Scheme 7). Carbazole is also considered to be a highly important N-heterocycle because of the ubiquity of its structural motif in numerous bioactive natural products, pharmaceutical agents, and diverse novel functional materials.[15] Indole products obtained via the present reaction pathway could

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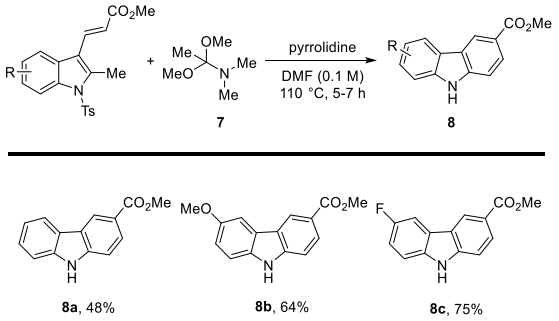
Scheme 7. Application of the Product for Carbazole Synthesis



[a]Reaction conditions: **2a**/**4c**/**4d** (0.2 mmol), *N*,*N*-dimethylformamide dimethyl acetal **7** (0.4 mmol), pyrrolidine (0.08 mL) under inert atmosphere. [b]Isolated yields, containing small amounts of *N*-methyl substituent of **8**, are reported.

be easily transformed to the corresponding functionalized carbazoles by a simple method.[16] Methyl 3-(2-methyl-1*H*-indol-3-yl)acrylates (**2a**, **4c**, and **4d**) with *N*,*N*-dimethylformamide dimethyl acetal (**7**) in pyrrolidine/DMF solution sequentially underwent cyclization to carbazole and detosylation, producing the corresponding functionalized N−H carbazoles. Both electron-donating −OMe (**8b**) and electron-withdrawing −F (**8c**) substituents were suitable for the transformation. Notably, carbazoles **8a** and **8b** are naturally occurring alkaloids.[17]

In conclusion, a synthetic route for accessing multifunctionalized indoles was developed through Ni-catalyzed *trans*-carboamination using 2-alkynylanilinoacrylate. C−N bond cleavage of a nickelacycle intermediate and *syn*/*anti*-rotation of the alkenyl-Ni intermediate are the key steps of this *trans*-carboamination. This approach allows the synthesis of 3-alkenyl indoles, which is otherwise challenging through the previous method that uses 2-alkynyl aniline derivatives. Notably, these functionalized indoles could undergo one-step conversion to the relevant carbazoles, another highly important N-heterocyclic compound, thus indicating the high utility of the product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03148.

Experimental details, analytical data of the synthesized compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(9) During the revision process, the indole synthesis was tried under the conditions used for benzofuran synthesis reported by the Arisawa group with tridentate TerPy ligand (ref 6b), but **2a** was not generated, indicating the ligand effect and different reactivity of N and O analogues.

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