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Rhodium-Catalyzed Atroposelective Construction of Indoles via C-H Bond Activation

Lincong Sun, Haohua Chen, Bingxian Liu, Junbiao Chang, Lingheng Kong, Fen Wang,* Yu Lan,* Xingwei Li*

Abstract: Reported herein is the rhodium(III)-catalyzed C-H activation of anilines bearing an N-isouquinolyl directing group for oxidative [3+2] annulation with four classes of internal alkynes, leading to atroposelective indole synthesis via dynamic kinetic annihilation with C-N reductive elimination constitutes the stereo-determining step. This reaction proceeds under mild conditions with high regio- and enantioselectivity and functional group compatibility.

Indoles are well-known structural motifs in a large number of natural products, pharmaceuticals, and organic materials.[1] In particular, axially chiral indoles have received increasing attention as prevalent chiral building blocks and ligands. Organocatalysis has offered powerful synthetic strategies to access axially chiral indoles.[2] They are alternatively accessed by metal catalysis (Scheme 1) following two synthetic strategies. Metal-catalyzed arylation of an existing indole ring at the 1-, 2-, 3- and 4-positions[3] (Scheme 1a) using hypervalent iodine reagents[3] aryl halides,[4] and quinones[4] induced axial chirality. In addition, functionalization of an arene[6] or olefin[7] group tethered to an indole also generated a C-N or C-C chiral axis. Alternatively, de novo construction of indole rings in an atropeoselective fashion has also been realized via cyclization of aniline-tethered alkynes (Scheme 1b). Thus, Kitagawa reported Pd-catalyzed cyclization of alkynes for synthesis of C-N axially chiral indoles.[8] Our group integrated C-H activation of sterically hindered indoles and alkyl cyclization for atroposelective synthesis of 2,3-biindolyl.[9] By using arylboronic acids as arylating reagents, Zhu realized Pd-catalyzed asymmetric Cacchi reaction of sterically hindered alkynes.[10] Nevertheless, metal-catalyzed de novo construction of chiral indoles remains highly rare. Our C-H activation approach to access axially chiral biindolyls[9] prompted us to take full advantage of C-H activation for construction of axially chiral biaryls. Two sub-strategies are followed, namely, de novo construction of a new chiral axis and dynamic kinetic transformation based on an existing axis,[11] with the latter being dominant. Nevertheless, most dynamic kinetic transformations convert an ortho C-H bond to a terminal group. The C-H activation-annulation approach, which increases molecular complexity, is more attractive. Waldmann reported intramolecular redox-neutral [4+2] annulation of benzamides bearing a pendant alkyne using a chiral JasCpRh(III) catalyst,[12] and our group recently developed an intermolecular version.[13] Meanwhile, Wang disclosed Rh(III)-catalyzed [2+2+2] carboannellation between N-arylindolinones and alkyne.[14] Nevertheless, these very few reports[12-14] are limited to 6,6-biaryl synthesis due to reactivity challenge posed by employment of bulky directing group and/or coupling reagent. The rarity of axially chiral indoles via C-H activation[15] is partially ascribed to the relatively low atropostability associated with pentatomic biaryls.[2g,9,11] Notably, Rh(III)-catalyzed C-H activation has allowed facile access to a large array of chiral products.[9,12-15] Inspired by Fagnou’s pioneering oxidative indole synthesis[16] and our own racemic system in 2010,[17] we aimed to apply C-H activation of anilines for atropmeric synthesis of N-isouquinolylindolines (Scheme 1c). Despite related racemic reports,[16-18] control of enantioselectivity can be challenging because this requires conformational control of the isouquinolyd directing group prior to C-N reductive elimination. We now report Rh(III)-catalyzed enantioselective [3+2] annulation between N-isouquinolinylamine and alkynes.

Aniline 1a was designed as an arene substrate, and its oxidative annulation with diphenylacetylene was optimized using Cramer’s[15a,b] Cp*Rh(III)/AgSbF$_5$ catalyst in the presence of a Ag(I) oxidant under very mild conditions[19] (Table 1). When catalyzed by (R)-Rh1, moderate to good ee but low yield of 3 was obtained when AgF, Ag$_2$O, AgOAc, or AgOPiv was used as an oxidant in THF, DCE, PhCl, or dioxane. Both the yield and ee were improved when the solvent was replaced by EtOAc with...
AgBF₄ as the oxidant (entry 5). Introduction of HOAc turned out to be beneficial to the enantioselectivity, and a 2:1 ratio of arene/alkyne further augmented the efficiency and enantioselectivity (entry 6). By lowering the catalyst loading to 4 mol%, product 3 was isolated in 62% yield and 92% ee (entry 14). In contrast, coupling using with the (R)-Rh2 and (R)-Rh3 catalysts only gave lower efficiency and enantioselectivity (Supporting Information).

Table 1. Optimization Studies. [a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>HOAc</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>AgOAc</td>
<td>THF</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>AgF</td>
<td>THF</td>
<td>42</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>AgF₂</td>
<td>THF</td>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>AgOPIv</td>
<td>THF</td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>AgBF₄</td>
<td>THF</td>
<td>44</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>HOAc</td>
<td>AgBF₄</td>
<td>THF</td>
<td>66</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>HOAc</td>
<td>AgBF₄</td>
<td>DCE</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>HOAc</td>
<td>AgBF₄</td>
<td>1,4-dioxane</td>
<td>35</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>HOAc</td>
<td>AgBF₄</td>
<td>PhCl</td>
<td>&lt; 5</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>HOAc</td>
<td>AgBF₄</td>
<td>tEOAc</td>
<td>50</td>
<td>89</td>
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<tr>
<td>11</td>
<td>HOAc</td>
<td>AgBF₄</td>
<td>tEOAc</td>
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<tr>
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<td>AgBF₄</td>
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<td>14</td>
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<td>AgBF₄</td>
<td>tEOAc</td>
<td>62</td>
<td>92</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: arene (0.05 mmol), alkyn (0.05 mmol), (R)-Rh1 (5 mol%), AgSbF₄ (20 mol%), oxidant (2.5 equiv), HOAc (2 equiv), solvent (1 mL), under Ar for 24 h. [b] Isolated yield. [c] Arene (0.1 mmol) was used (48 h). [d] Without AgSbF₄. [e] (R)-Rh1 (4 mol%) and AgBF₄ (16 mol%) were used.

With the optimized reaction conditions in hand, the scope of the alkyn was next explored with aniline 1a as an arene substrate (Scheme 2). Symmetrical diarylalkynes bearing alkyl, OMe, and halogen substituents at the para position coupled in consistently good yield and excellent enantioselectivity (86-96% ee, 3-9), while introduction of a para CF₃ tends to give diminished enantioselectivity (10). Additionally, scale-up synthesis of 3 (1 mmol) was successful, with essentially no deterioration of enantioselectivity. Comparable efficiency and enantioselectivity (84-93% ee) were also realized for a series of meta-substituted alkynes (11-14). While ortho-substituted alkynes generally exhibited poor efficiency due to steric effect, presence of ortho F groups in the alkyn was tolerated (15). Extension of the alkynes to disubstituted and to heteroaryl ones was also successful (16-18, 93-95% ee). The absolute configuration of product (R)-18 has been determined by X-ray crystallography (CCDC 2032437). Moreover, symmetrical dialkyl alkynes were amenable to this annulation system (19 and 20). Extension to alkyl-aryl alkynes ones met with difficulty under the original conditions. Gratifyingly, by replacing the AgBF₄ oxidant with AgOPIv, the coupling of alkyl-aryl alkynes proceeded in high enantioselectivity and in good to excellent regioselectivity (21-24). Extension of simple alkyl group in the alkyn to ether- and silyl ether-alkyl groups gave excellent regioselectivity and generally high enantioselectivity (25-30). A chloroaryl-substituted alkyn coupled with lower regioselectivity (31) although the enantioselectivity remained high.
To better define the scope of the anilines, substituted 1,3-enynes were explored (Scheme 2). It was found that employment of either AgBF₄ or AgOPiv oxidant failed to give excellent enantioselectivity. To our delight, CH₂SO₂Ag proved to be an superior oxidant in THF solvent. Thus, the coupling of enyne bearing different alkyl and (hetero)aryl groups afforded the [3+2] annulation product in generally high yield, high (>11:1 r.r.) regioselectivity, and excellent (89-96% ee) enantioselectivity (32-38).

The scope of the aniline was next investigated (Scheme 3). Introduction of a B-CI group to the isoquinoline ring allowed the coupling with diarylacetylenes in comparably or higher yield and enantioselectivity (39-43). Variation of the 8-substituent to -Me and -Ph group in the isoquinoline ring afforded consistently high enantioselectivity (45 and 46). However, moderate enantioselectivity and low efficiency were obtained for the 8-methoxy N-isoquinloylaniline. Examination of para-meta-substituent in the aniline revealed compatibility of alkyl, aryl, and halogen groups (47-56). Aniline bearing an ortho OMe group also coupled with attenuated enantioselectivity (57). Of note, coupling of 8-unsubstituted isoquinolylaniline bearing an ortho-Me group with diphenylacetylene under modified conditions using AgOTf as an oxidant afforded product 58 in 65% yield and 84% ee, although its barrier of racemization is relatively low.

Derivatization reactions have been carried out for product 3 to demonstrate the synthetic utility (Scheme 4). Treatment of 3 with NBS led to selective bromination at the 6-position of the indole ring (55). Suzuki coupling with p-TolB(OH)₂ afforded product 59, and the Sonogashira reaction using different alkenes gave products 60 and 61 in good yields. Hydrogenation of 32 afforded product 62 and oxidative C=C cleavage gave product 63. Methylation of isoquinoline 3 afforded the isoquinolinium salt 64 in excellent yield.

Preliminary mechanistic studies have been conducted (Scheme 5). H/D exchange between 1a and CO₂CD₂O under slightly modified conditions in the presence or absence of alkyne 2a all gave significant deuteration at the ortho positions of the anilines, suggesting reversible C-H activation (Scheme 5a). Parallel KIE experiments were then conducted. A rather large value of kᵣ/k₀ = 4.9 indicated that C-H cleavage is involved in the turnover-limiting step (Scheme 5b). Attempts to prepare a rhodacylic intermediate failed. Theoretical studies at the DFT level have been then conducted to explore the asymmetric induction mode of this coupling reaction. We examined the enanto-determining reductive elimination of four possible rhodacycles with different orientations of the arene and the DG together with a prochiral C-N axis, which occurs via four possible transition states TS-R-1, TS-R-2, TS-S-1, and TS-S-2 (Scheme 5c). It was found that the lowest energy reductive elimination that forms the (R) and (S)-product were defined by transition state TS-R-1 and TS-S-2, respectively. The transition state TS-R-1 is 5.8 kcal/mol lower than TS-S-2, which is consistent with our observed (R) selectivity. Optimized structure analysis shows that in transition state TS-S-2, due to steric repulsion between the methoxy group in chiral ligand and phenyl group of styrene skeleton, the torsional dihedral angle of the phenyl group in styrene skeleton is higher than that of TS-R-1 (147.4° vs 115.3°). We also examined the coordination of arene or alkyne substrate to the corresponding five-coordinate Rh(III) complex. However, neither the thermodynamics of ligation nor the kinetic barrier of RE is favorable. At this stage we cannot rule out possibility of competitive RE of Rh(IV) species in the catalytic cycle. [20]
In summary, we have realized Rh-catalyzed C-H activation of N-isouquinolylamines en route to annulation with a wide scope of internal alkynes for atroposelective synthesis of N-isouquinolylindoles in high regio- and enantioselectivity. In contrast to previous dynamic kinetic transformations, this [3+2] annulation utilized an amino atom (nitrogen) as a reaction site. Preliminary DFT studies indicate that the asymmetric induction mode may involve reductive elimination of two diastereomeric Rh(III) alkynyl species. This atroposelective synthesis of heterocycles may find applications in construction of complex functional molecules. Future work will focus on full mechanistic studies of this coupling system.

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Conflict of interest

The authors declare no competing financial interest.

Keywords: rhodium • aniline • alkynie • indole • axial chirality


C-H activation of N-isoquinolylanilines catalyzed by chiral rhodium(III) cyclopentadienyls has been realized in [3+2] annulation with four classes of internal alkynes under mild oxidative conditions allowed atroposelective synthesis of biaryl indoles in high regio- and enantioselectivity (> 50 examples, 71-96% ee).