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Communication

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Ruthenium-Catalyzed Enantioselective C–H Functionalization: A Practical Access to Optically Active Indoline Derivatives

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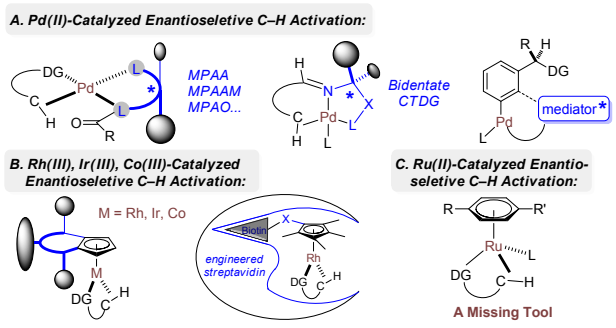
Supporting Information Placeholder

ABSTRACT: Ru(II)-catalyzed enantioselective C–H activation/ hydroarylation has been developed for the first time, allowing for highly enantioselective synthesis of indoline derivatives via catalytic C–H activation. Commercially available Ru(II) arene complexes and chiral *α*-methylamines were employed as highly enantioselective catalysts. Based on a sterically rigidified chiral transient directing group, multi-substituted indolines were produced in up to 92% yield with 96% ee. Further transformation of the resulting 4-formylindoline enables access to an optically active tricyclic compound that is of potential biological and pharmaceutical interest.

Development of new catalytic systems for enantioselective C–H functionalization has been growing rapidly with multidisciplinary impacts.[1] Among different approaches,[2] directed C–H bond activation has emerged as a general and effective tool.[3] Beyond the C–H oxidative addition-based pathways,[1b,2b,4] mechanistically new reactivities and selectivities by high-valent metals, including Pd(II),[3a-c,5] Ru(II),[6] Rh(III),[7] and others,[8] have emerged via metalation/deprotonation pathways. Unlike low-valent metal-catalyzed systems,[1b] their enantioselective versions encounter mechanistic complication and intrinsic challenges that make many "privileged" ligands incompatible.[5a,9]

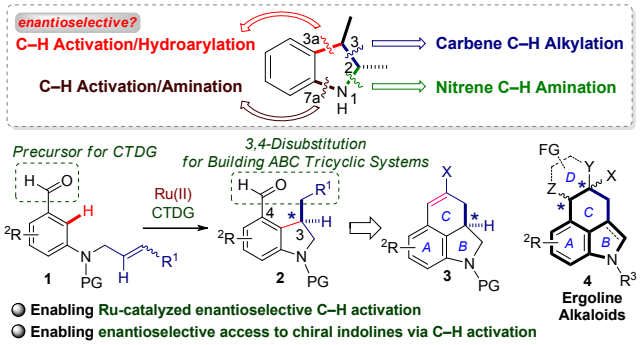
Scheme 1. Transition Metal Catalysts for Enantioselective C–H Activation via Directed Metalation/Deprotonation



During the past decade leading efforts by the Yu group have enabled successful application of monoprotected amino acids (MPAA) and related ligands in Pd(II)-catalyzed enantioselective C–H activation (Scheme 1, A).[5a,10] Pioneered by Yu recently, bidentate chiral transient directing groups (CTDGs)[10e,11] and chiral transient mediators[12] have been developed to address major challenges. The conformationally organized intermediates resulting from the chelation of the MPAA ligands and CTDGs at the square planar Pd center are key to the superior enantiocontrol. Moreover, Rh(III)-catalyzed enantioselective processes have been accomplished by the Cramer group with chiral Cp* ligands[13] and the Rovis group with engineered enzymes,[14] respectively (Scheme 1, B). While Rh(III) serves as the major focus of d^6 metal catalysts with continued development,[9a,15] the scope was also extended to Ir(III)[1b,16] and very recently, Co(III)[17]. Sharing the general C–H metalation step, each metal species has shown distinct stereoselectivity and reactivity profiles, which have brought in new opportunities for the enantioselective access to various target molecules.[18]

During the past two decades, Ru(II) arene complexes have emerged as effective and favorable catalysts for C–H activation owing to their cost-effectiveness, easy preparation, versatile and distinct reactivity and selectivity.[2i,6b-f,19] Nevertheless, enantioselective C–H activation with Ru(II) remains unknown (Scheme 1, C).[1b,20] With only three coordination sites, Ru(II) arene catalysts are not readily compatible with the design of ligands or bidentate CTDGs for Pd.[9b] Meanwhile, the inactivity of the Ru(II)Cp complexes in C–H activation has limited the application of chiral Cp* ligands.[21] While Ru(II) continues to advance as an active metal catalyst for C–H activation, developing enantioselective versions as new synthetic tools is highly desirable as this would unlock practical and inexpensive access to meet the increasing need for new optically pure structures.

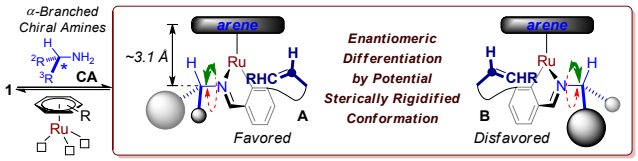
Scheme 2. Indoline Formation via C–H Functionalization



Optically active indolines are important motifs in both synthetic and medicinal chemistry.[22] C–H activation and functionalization have enabled approaches that are capable of constructing any of the four non-aromatic bonds (Scheme 2). The enantioselective formation of C2–C3 and C2–N1 bonds can rely on carbene C–H alkylation[23] and nitrene C–H amination,[24] respectively. While the Pd(II)-catalyzed C–H activation was successful for making the C7a–N1 bond,[25] which does not generate chirality, the

hydroarylation via C–H activation provides a pathway to enantioselectively construct the C3–C3a bond. While enantioselective hydroarylation has been successfully developed for the syntheses of other related cyclic skeletons, the enantioselective synthesis of indolines has been underdeveloped.[1b,7b,7c,26,27] Of particular relevance, Bergman and Ellman demonstrated a synthesis of a functionalized dihydrofuran in 45% ee using 30 mol% of a chiral amine co-catalyst in a Rh(I)-catalyzed intramolecular hydroarylation.[27c] Recent disclosure of Ru(II) as an effective catalyst for intramolecular hydroarylation encourages the development of the potential enantioselective processes.[28] Considering the cost-effectiveness and the availability of the simple Ru(II) arene complexes, identifying a suitable imine-based CTDG strategy seems practical. Starting with benzaldehyde **1**, the resulting 3,4-disubstituted indolines **2** are particularly desirable as they allow for cyclization with the 4-formyl group, which produces tricyclic skeleton **3** that is relevant to the synthesis of ergot analogs (**4**).[22c,29]

Scheme 3. Postulated Asymmetric Induction Model



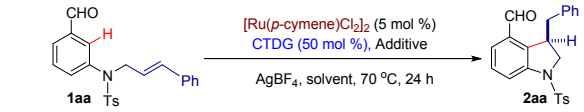
Since only monodentate TDGs may work with Ru(II) arene catalysts, we envisioned chiral α-branched amines **CA** with an α-hydrogen would be adaptable (Scheme 3). Suggested by the measurement on a known structure,[30] the distance between the nearly parallel C–N bond and arene unit in a proposed key intermediate **A** may be ~3.1Å. The limited distance would restrict the free rotation of the C–N bond in the postulated intermediates **A** and **B**, with the hydrogen briefly facing the top arene. This amine-arene rigidified conformation would make a stationary arrangement of the big and small substituents on two sides of the ruthenacycle. During the enantio-determining insertion step,[13] the alkene would approach with the less substituted side toward the top arene, and the double bond would approach from the less hindered side of the stereogenic carbon center to form the favored enantiomer.

As an initial study, herein we report the first Ru-catalyzed enantioselective C–H activation/hydroarylation reaction and its synthetic application for an ergot alkaloid-relevant tricyclic structure. It enables a highly enantioselective synthesis of indolines via catalytic C–H activation. Readily available Ru(II) complexes and chiral α-methylamines are employed as catalysts and afforded various chiral 4-formylindolines in up to 96% ee.

Initial efforts focused on the hydroarylation of *m*-amidobenzaldehyde **1aa** with $[Ru(p\text{-cymene})Cl_2]_2$ and $AgBF_4$ in 1,2-dichloroethane (DCE) (Table 1). Acetic acid (5 equiv) was used for accelerating both the C–H activation and the reversible imine formation. At 70 °C, chiral cyclic amine **CA1** afforded indoline **2aa** in 35% yield and 17% ee (entry 1). Chiral amines **CA2** and **CA3** were shown to be ineffective, presumably due to additional coordination by the OH and NH units (entries 2 and 3). With a protected NH (**CA4**), the reaction occurred with 33% ee, however, in low yield (entry 4). Productive reactions were observed with α-methylbenzylamine analogs **CA5**–**CA9**, and a general trend in enantiocontrol has emerged (entries 5–9). Increased steric hindrance at the *ortho*-position of the phenyl, presumably orienting toward the reaction center, led to increases in enantioselectivity. Notably, all (*R*)-amines gave the same sense of asymmetric induction, which is consistent with the proposed model (Scheme 3).

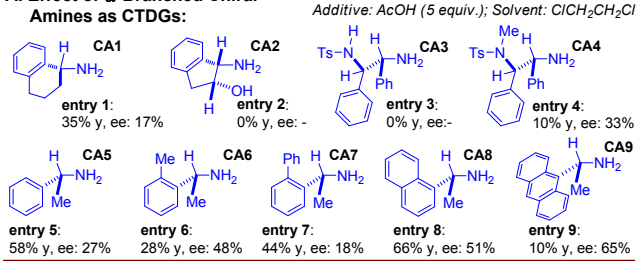
Toluene as the solvent was later found to offer higher enantiocontrol but decreased yield with chiral amine **CA8** (entry 10). A mixed solvent system with toluene and hexafluoroisopropanol (HFIP) turned out to be effective in conjunction with KH_2PO_4 as an additive. This condition requires only catalytic amount of the carboxylic acid, thus making the employment of some functionalized acids practical.[15f,16,17b,31] A 30 mol % of bulky acids **A1** and **A2** effectively increased both yield and ee, respectively (entries 11 and 12). Examination of other *N*-protected amino acids (entries 13–19) afforded **2aa** in 76% yield and 84% ee (entry 17). With protected L-*tert*-leucine (**A7**), further optimization resulted in 88% yield of **2aa** in 94% ee in PhCl/HFIP solvent at 60 °C (entries 20 and 21). Notably, the sense of the chiral induction is predominantly determined by the chiral amine, as evidenced by the resulting -85% ee with ent-**CA8** and **A7** (entry 22).

Table 1. Ru(II)-Catalyzed Enantioselective Hydroarylation under Various Conditions[a]



A. Effect of α-Branched Chiral Amines as CTDGs:

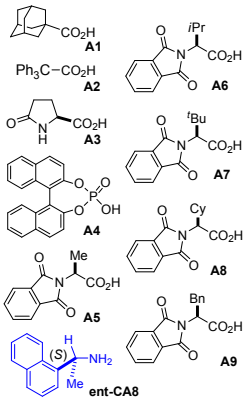
Standard conditions:
Additive: AcOH (5 equiv.); Solvent: ClCH$_2$CH$_2$Cl



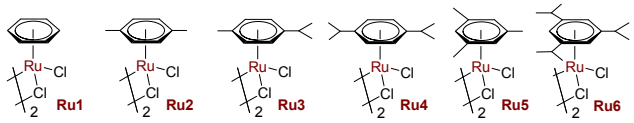
B. Effect of Additives and Solvents:

*Standard conditions: CTDG: **CA8***
A1-9 (30 mol%) & KH_2PO_4 (2 equiv.)

entry	additive	solvent	yield (%)[b]	ee (%)
10	AcOH	PhMe	37	66
11	**A1** & KH_2PO_4	PhMe:HFIP	52	75
12	**A2** & KH_2PO_4	PhMe:HFIP	50	79
13	**A3** & KH_2PO_4	PhMe:HFIP	27	35
14	**A4** & KH_2PO_4	PhMe:HFIP	17	40
15	**A5** & KH_2PO_4	PhMe:HFIP	52	79
16	**A6** & KH_2PO_4	PhMe:HFIP	74	81
17	**A7** & KH_2PO_4	PhMe:HFIP	76	84
18	**A8** & KH_2PO_4	PhMe:HFIP	53	81
19	**A9** & KH_2PO_4	PhMe:HFIP	44	76
20	**A7** & KH_2PO_4	PhCl:HFIP	89	91
21	**A7** & KH_2PO_4	PhCl:HFIP	88	94
22[c]	**A7** & KH_2PO_4	PhCl:HFIP	68	-85



C. Effect of Arene Ligands: *Standard conditions:*
*CTDG: **CA8**,* **A7** (30 mol %) & KH_2PO_4 (2 equiv.), PhCl:HFIP

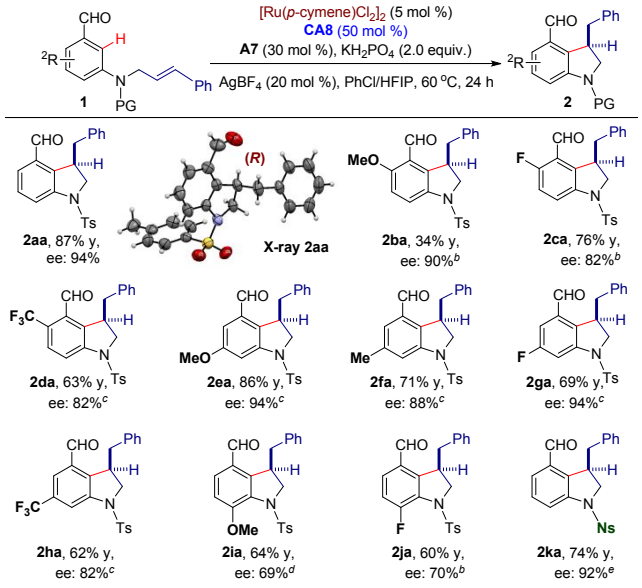


[a]**1aa** (0.05 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgBF_4$ (20 mol %), acid (30 mol %), chiral amine (50 mol %),[32] KH_2PO_4 (2.0 equiv), solvent 0.4 mL, 24 h. [b]Determined by ^1H NMR with $PhNO_2$ as internal standard. [c]ent-**CA8** was used.

Based on the postulated model of enantiocontrol, the sterics of the arene ligands would make an impact. A clear trend showed that increasing steric bulkiness on the arene led to improved enantioselectivity (entries 23–26), although trisubstituted arene ligands deactivated the catalysts (entries 27 and 28).

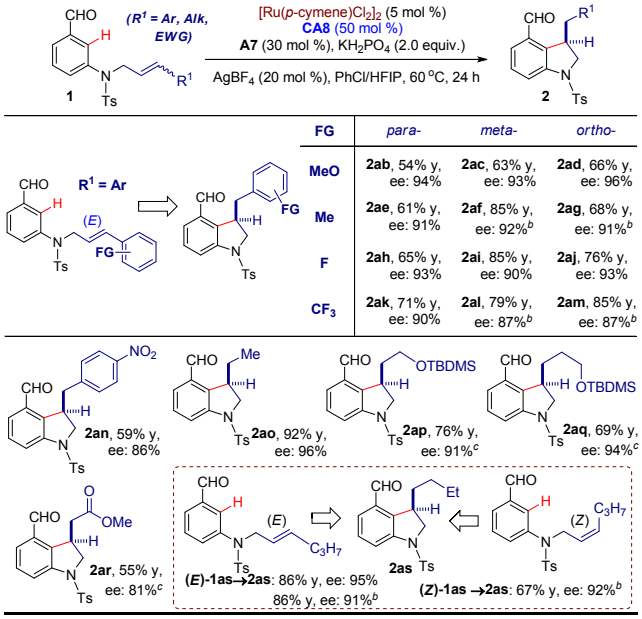
Under the optimized conditions, various substituents on the benzaldehyde unit of **1** were studied (Table 2). The *R* configuration of **2aa** was confirmed by single-crystal X-ray diffraction. The *ortho*-substituents to the aldehyde would have significant influences both sterically and electronically. As demonstrated by **2ba**–**2da** with MeO-, F-, CF_3- groups, respectively, electronically and sterically different *ortho*-functional groups were well tolerated at slightly elevated temperature. The *meta*-substituents, being *para*- to the reacting C–H bond, would electronically influence both C–H activation and insertion steps. Remarkably, **1** with electron-donating and withdrawing, alkyl, and halogen groups were all fruitfully transformed to indoline **2ea**–**2ha** with up to 94% ee. Moreover, when a methoxy group and a fluorine atom were located on the *para*-position, catalytic reactions were also performed smoothly and enantioselectively (**2ia** and **2ja**). Moreover, an *N*-nosyl group was successfully tolerated, as demonstrated by the production of **2ka** in 74% yield and 92% ee.

Table 2. Ru(II)-Catalyzed Enantioselective Hydroarylation with Various Arene Moieties[a]



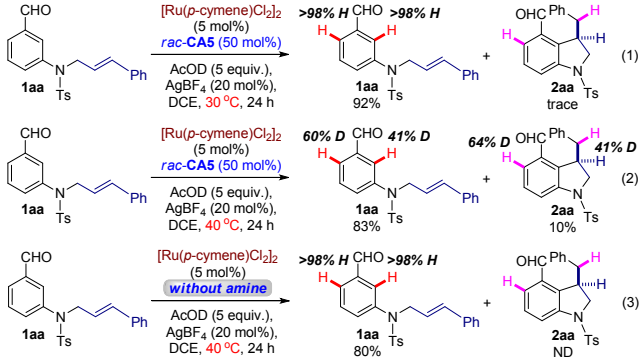
[a]**1** (0.1 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgBF_4$ (20 mol %), acid (30 mol %), chiral amine (50 mol %), KH_2PO_4 (2.0 equiv), solvent 0.8 mL, 60 °C, 24 h. Isolated yield. [b]80 °C. [c]70 °C. [d]90 °C. [e]48 h.

Table 3. Ru(II)-Catalyzed Enantioselective Hydroarylation to Various Alkenes[a]



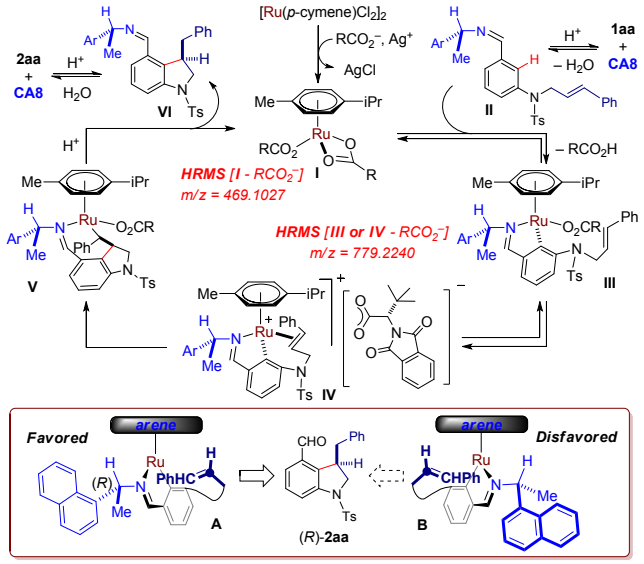
[a]Same conditions as table 2. [b]70 °C. [c]48 h.

Subsequent efforts went on with amidobenzaldehyde **1** bearing different types of internal alkene units (Table 3). Respectively, (*E*)-styrenyl groups containing MeO-, Me-, F-, CF_3-, NO_2- groups at all possible positions were systematically investigated and afforded the corresponding indoline **2** in up to 85% yields with ee values mostly above 90% (**2ab**–**2an**). Aliphatic alkenyl groups were also effective substituents for producing **2ao**—**2aq** in good yields with up to 96% ee. Remarkably, the catalytic system was successful with electron-deficient alkene units, as exemplified by the formation of **2ar** from the corresponding acrylate-containing benzaldehyde. Additionally, the performances of the *E* and *Z* isomers were compared. At 70 °C, (*E*)-**1as** produced the same product **2as** in higher yield than (*Z*)-**1as**, while their ee values were almost the same, indicating the configuration of the internal alkene was not decisive for the enantiocontrol.[33] Finally, slightly lower temperature for the reaction of (*E*)-**1as** produced indoline **2as** with 95% ee.



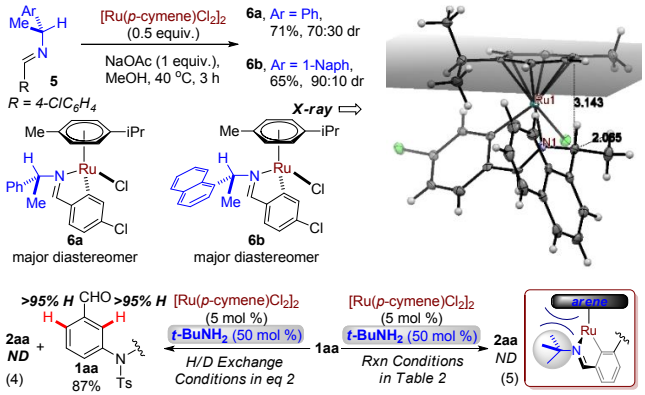
For probing the mechanism, H/D exchange reactions were carried out with the racemic form of amine **CA5** in DCE. Reversible H/D exchange did not occur at 30 °C. In contrast, at 40 °C, significant H/D exchange was observed in both the product and recovered **1aa** (eqs 1 and 2). Moreover, a control reaction without amines gave neither the product **2aa** nor detectable C–H activation (eq 3).

Scheme 4. Postulated Mechanism and Enantiocontrol



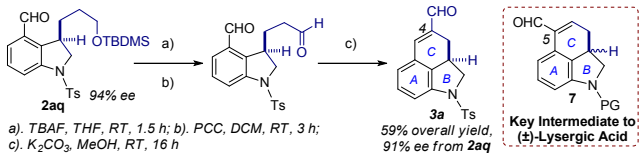
Based on data above and results from an existing study,[6b] a proposed mechanism is formulated to begin with a reversible Ru(II)-based C–H activation of the transient imine intermediate **II** in acidic media, forming ruthenacycle **III** (Scheme 4). Besides assisting the metalation/deprotonation step, the bulky carboxylate presumably forms an ion pair with the cationic part of the intermediate **IV**, which would count for their observed impact on the enantiomeric control. HRMS study on the reaction system indicated a major species matching the intermediate **I** without a carboxylate anion, and another major species matching the cationic part of either intermediate **III** or **IV** (see SI for details). Based on the postulated asymmetric induction model, the alkene unit should prefer to approach the Ru center from the same side of the conformationally rigidified methyl group on the chiral carbon (Scheme 4, **A** and **B**). Notably, the proposed model leads to the *R* configuration of the chiral center in **2aa**, which is in accord with the observation from its single crystal.

Scheme 5. Syntheses of Intermediate-related Ruthenacycles



To understand the asymmetric induction, chiral imines **5** was converted to ruthenacycles **6** as simplified models to the key intermediate **III** (Scheme 5). The single crystal structure of **6b** confirmed the α-hydrogen of the chiral amine moiety indeed faced the top arene. The perpendicular distance from the chiral carbon to the arene plane appears to be 3.143Å, while the distance from the chiral carbon to the hydrogen center of the α-methyl group is 2.065Å. The comparison suggests even a CH_3- group may sterically restrict the rotational freedom of the C–N bond. Consistent with this notion, both H/D exchange (eq 4) and catalytic reactions (eq 5) employing *tert*-butylamine resulted in barely any H/D exchange and no indoline product.

Scheme 6. Synthetic Applications of the Indolines



Chiral indolines serve as important precursors for constructing complex structures. ABC tricyclic aldehyde **7** is a key intermediate for building the D ring in the synthesis of (±)-lysergic acid (Scheme 6).[29e-h] Terminal group modification of indoline **2aq** followed by an aldol condensation with the 4-formyl group afforded tricyclic **3a** in 91% ee. Different from the 5-formyl group in **7**, **3a** would open potential asymmetric access to new non-naturally occurring ergot analogs.[22c]

In summary, Ru-catalyzed enantioselective C–H activation/hydroarylation reaction has been developed for the first time. The cooperation of the α-methyl chiral amine has enabled an effective application of enantioselective C–H activation for synthesis of indoline derivatives. The new system features practicality with the employment of the commercially available and cost-effective Ru(II) complex and chiral amine. This method provides opportunities for the enantioselective access to various indoline-based bicyclic and polycyclic structures. More broadly, the process represents a new tool that would stimulate further exploration of enantioselective C–H functionalization reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details and analytical data for all new compounds (PDF); Crystallographic data (CIF).

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Notes

The authors declare no competing financial interests.

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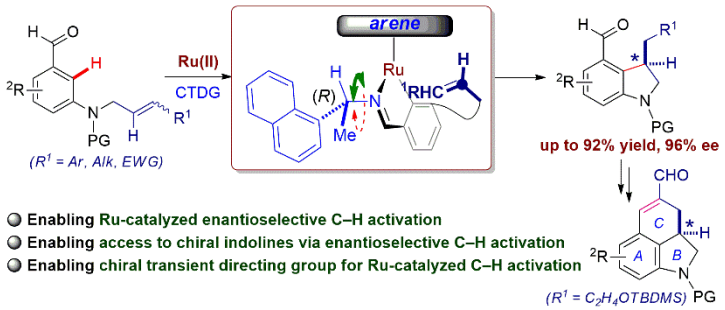

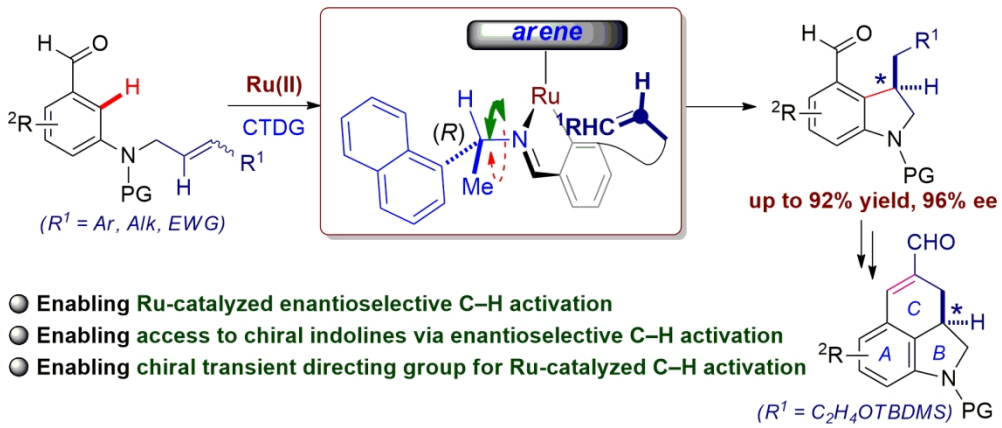

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