# Co(III)-Catalyzed Coupling of Enaminones with Oxadiazolones for Imidazole Synthesis

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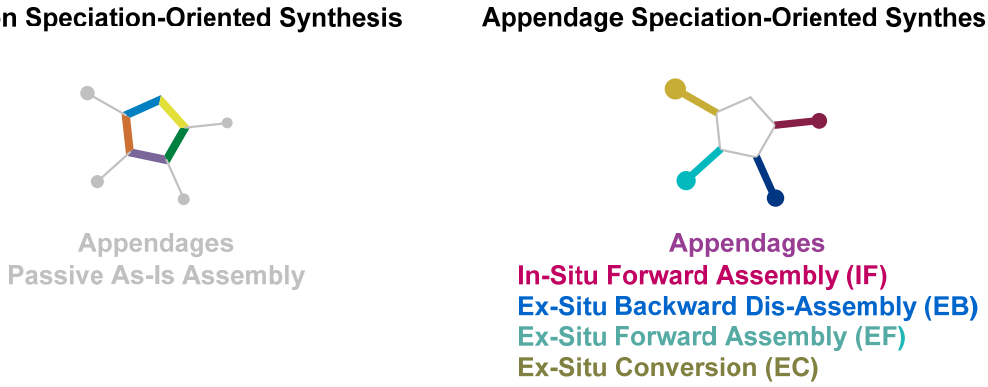
**Abstract:** Skeleton speciation-oriented synthesis as the conventional wisdom of synthetic methodology development prioritizes skeleton as the center of attention for organic speciation, the creation of organic species with differentiated structure-defining feature. The passive as-is assembly of appendages as a secondary accessory inevitably leads to the convergence of appendage pattern on skeleton. We report herein a synthetic practice of appendage speciation-oriented synthesis, emphasizing appendages as the focal point for organic speciation. This synthetic modality seeks, proactively, the maximization of type-, position-, and configuration-variance of appendages through both in situ and ex situ appendage speciation. A Co(III) catalytic protocol in accord with this synthetic modality has been established for coupling of enaminones and oxadiazolones to imidazoles, allowing the achievement of full position-variance of appendages. This translates to expanded reaction and structural development scope and can provide a fertile ground for productive organic synthesis.

**Keyword:** Organic Speciation; Skeleton Speciation-Oriented Synthesis; Appendage Speciation-Oriented Synthesis; Cobalt Catalysis; Imidazole

Organic synthesis is at the heart of modern science for its structure- and accordingly function-delivering capability.[1-7] An incessant source of inspiration for invigorating this enabling tool is innovative synthetic methodology development. Synthetic methodology development is a foundational systemic practice for synthetic organic speciation, the creation of organic species with differentiated structure-defining feature. In this regard, conventional synthetic methodology development for each individual working protocol is frequently focused on skeleton speciation-oriented synthesis (Scheme 1):[8-10] a synthetic modality that prioritizes synthetic organic speciation by the key bond transformation event and the correspondingly forged primary skeleton, with the associated peripheral appendages (H substituent is considered as an appendage herein, but only non-H appendages are explicitly enumerated for convenience) viewed as a secondary accessory. This skeleton speciation-oriented synthesis has contributed constructively to organic synthesis for entry into structural and functional space of interest. Albeit largely operational, a major drawback for this synthetic modality is limited reaction and structural development scope in the two application settings due to

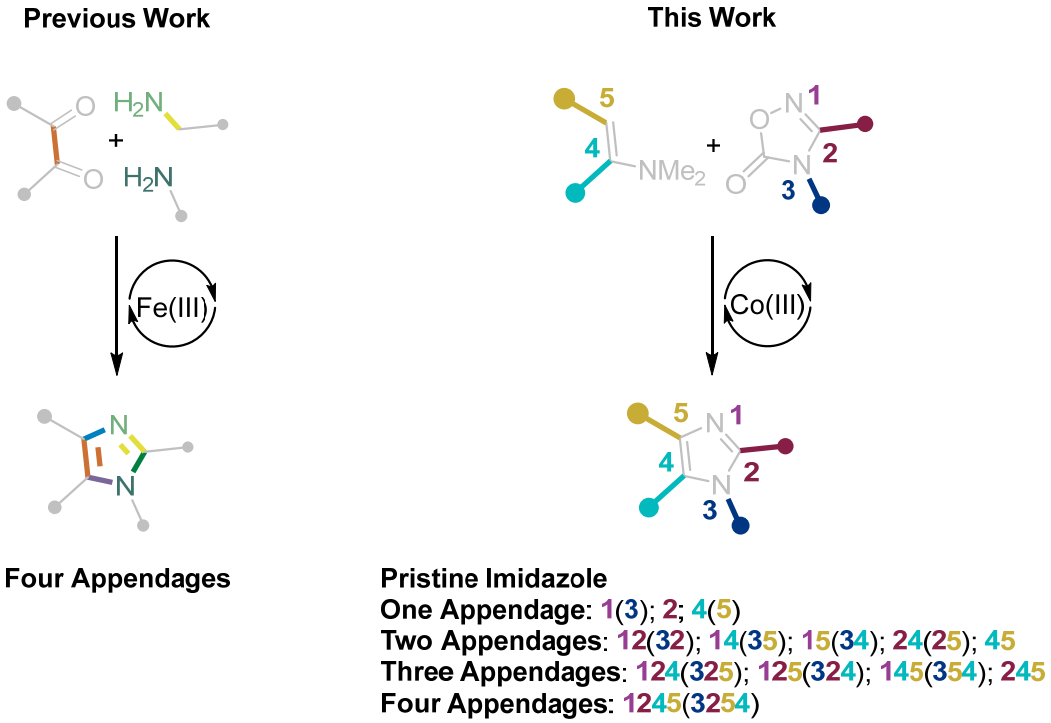
**Scheme 1. Skeleton Speciation-Oriented Synthesis (Conventional Synthetic Methodology Development Modality) and Appendage Speciation-Oriented Synthesis (Synthetic Methodology Development Modality Reported Herein).**



the passive as-is assembly of converged appendage pattern on skeleton. In our view, a more effective strategy for synthetic methodology development is appendage speciation-oriented synthesis (Scheme 1): a synthetic modality that prioritizes synthetic organic speciation primarily by the peripheral appendages in line with the key bond transformation event and subsequent peripheral bond manipulation, with the skeleton viewed as a secondary accessory. A central logic of appendage speciation-oriented synthesis is to proactively seek the maximization of position-, type-, and configuration-variance of appendages through both in situ appendage speciation (forward assembly of appendages in concomitance with the key bond transformation, or IF) and ex situ appendage speciation (subsequent to the key bond transformation, backward dis-assembly of assembled appendages to H substituent, or EB, forward assembly of appendages from H substituent, or EF, and conversion of appendages, or EC). Through the fundamental transition of synthetic logic, this synthetic modality can usher in the diverged appendage pattern on skeleton as a versatile synthetic handle for more productive access to expanded reaction and structural development scope. With this prospect in mind, herein, we report Co(III) catalytic coupling of enaminones (enaminoesters are considered as part of the category) with oxadiazolones for appendage speciation-oriented synthesis of imidazoles (Scheme 2).

Imidazoles are an important class of organic compounds with significant implications in pharmaceutical chemistry[11-14] and materials science.[15-18] Synthetic methodology development has continued relentlessly over the past century for the construction of these privileged structured motifs. Collectively, these massive efforts

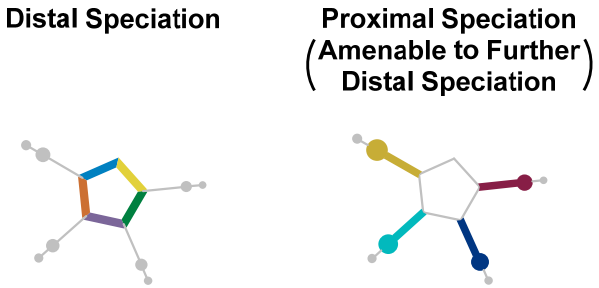
**Scheme 2. A Typical Example for Skeleton Speciation-Oriented Synthesis of Imidazoles (Previous Work) and the Appendage Speciation-Oriented Synthesis Method (This Work).**




have led to the establishment of an assortment of working protocols, with bonding sites at, for example, C2-N3, N1-C2/C4-C5, N1-C2/N3-C4, N1-C2/C2-N3, N1-C5/N3-C4, N1-C5/C2-N3, N1-C5/N3-C4/C4-C5, N1-C2/N1-C5/N3-C4, N1-C2/C2-N3/N3-C4, N1-C2/C2-N3/N3-C4/N1-C5 (note: 1*H*, on N1, and 3*H*, on N3, tautomers can exist and only one tautomer is presented herein; the numbering of atoms can be reciprocal with respect to N1 and N3, in conjunction with C4 and C5).[19-37] Each of these protocols invariably follows the synthetic logic of skeleton speciation-oriented synthesis. Indeed, appendages are typically not explicitly considered in synthesis, except in the context of supporting the formation of skeleton. For example, statistically, a disproportionally number of the protocols mandate the presence of three or four appendages to afford imidazoles[38-42] (Scheme 2). These position-fixed appendages can not only frequently be unintended substituents but also block the flexibility for intended structural

elaboration, thus vastly mitigating the significance of the protocols. Herein we illustrate the concept of appendage speciation-oriented synthesis by a prototypical demonstration of the achievement of full position-variance of appendages for imidazoles (pristine imidazole; one appendage: 1(or equivalently, 3), 2, 4(5); two appendages: 12(32), 14(35), 15(34), 24(25), 45; three appendages: 124(325), 125(324), 145(354), 245; four appendages: 1245(3254)) (Scheme 2). This proximal speciation (distance in reference to the skeleton) (Scheme 3) is in essence an appendage display method that can present spatially diverged variants; in contrast, distal speciation (Scheme 3) only allows the generation of spatially converged variants. Four crucial factors contribute to the success of this endeavor: polarity matching-permitted N1-C5/N3-C4 bonding (enaminone: C5/C4; oxadiazolone: N1/C2/N3), position variability of appendages (on C5 or C5/C4, on C2 or C2/N3, for IF), compatibility of ester group (on C5 and/or C2, for EB), and site-specific reactivity (for EF).

**Scheme 3. Distal Speciation (Previous Work) and Proximal Speciation (This Work).**



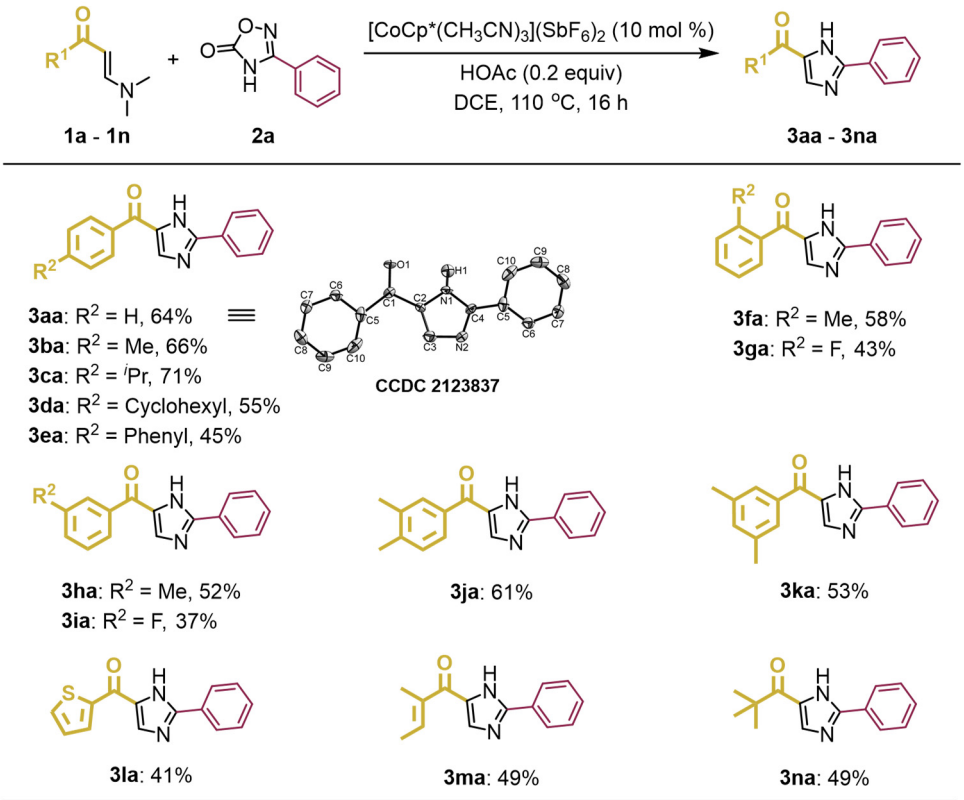

We commence the experimental investigation by reacting (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**1a**) with 3-phenyl-1,2,4-oxadiazol-5(4*H*)-one (**2a**). The screening of catalytic condition at the 0.20 mmol reaction scale identifies $[CoCp^*(CH_3CN)_3](SbF_6)_2$ as a viable catalyst precursor for the synthesis of phenyl(2-

phenyl-1*H*-imidazol-5-yl)methanone (**3aa**; with the structure unambiguously determined by single-crystal X-ray diffraction). **3aa** can be obtained in 32% yield under 3 mol% $[CoCp^*(CH_3CN)_3](SbF_6)_2$ catalysis after 16 h of 110 °C reaction in dichloroethane (DCE). The inclusion of 0.5 equiv HOAc raises the product yield to 42%; with NaOAc, the yield drops to the trace. An increase of HOAc quantity to 5.0 equiv decreases the yield to 22%. A combination of 5 mol% $[CoCp^*(CH_3CN)_3](SbF_6)_2$ and 0.5 equiv HOAc gives a yield of 46%. The yield can be further boosted to 55% with 10 mol% $[CoCp^*(CH_3CN)_3](SbF_6)_2$. An optimized yield can reach 64% with the adjustment of HOAc quantity to 0.2 equiv. Gratifyingly, under this optimized condition, a scale-up reaction at the 1.0 mmol level maintains a yield of 60%. An extra inclusion of 1.0 equiv $Cu(OAc)_2$ trims the yield to trace; the change of 10 mol% $[CoCp^*(CH_3CN)_3](SbF_6)_2$ to 10 mol% $[CoCp^*(CO)I_2]$/0.2 equiv $AgSbF_6$ also negatively impacts the yield (28%). In addition, an alteration of reaction temperature to 80 °C (<10% yield), 100 °C (52% yield), and 120 °C (58% yield) is not beneficial.

With the experimental condition optimized, we then set out to inspect the substrate scope from the conventional skeleton speciation-oriented synthesis perspective. The enaminone side is first examined, with **2a** as the coupling partner (Scheme 4). The reaction can proceed well with **1a** phenyl *para*-substituted. The product yield slightly goes up with Me (**1b**, 66%) and $^i$Pr (**1c**,71%), and goes down with cyclohexyl (**1d**, 55%) and phenyl (**1e**, 45%). The reaction is also tolerant of both electron-donating and electron-withdrawing *ortho* (Me, **1f**, 58%; F, **1g**, 43%) and *meta* (Me, **1h**, 52%; F, **1i**, 37%) substitutions, albeit destined for progressively lower yield. For the disubstitution,

the *para*, *meta* one (**1j**, 61%) is superior to the *meta*, *meta* one (**1k**, 53%). The replacement of **1a** phenyl with thiophen-2-yl (**1l**, 41%), but-2-en-2-yl (**1m**, 49%), and $^{t}$Bu (**1n**, 49%) reduces the yield. It should be noted that this substrate scope survey is conducted in a typical distal speciation modality for synthetic methodology development: the appendage type and position are fixed (2, phenyl; 5, carbonyl) at the immediate neighboring site to skeleton, and the variant feature emerges only from appendage distinction at the distal site (further away from the carbonyl); these species thus share a closely resembled spatial feature.

**Scheme 4. Substrate Scope of Enaminones from the Conventional Perspective.**[a][b]

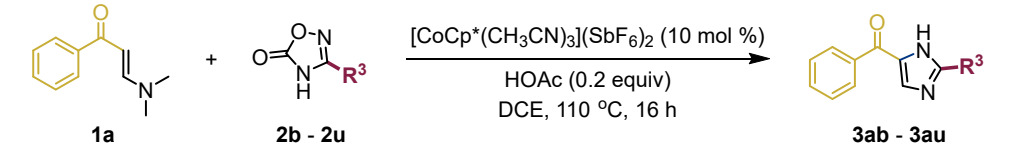


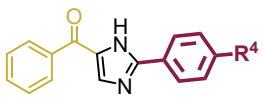

[a]Reaction condition: compounds **1a** - **1n** (0.24 mmol, 1.2 equiv), **2a** (0.2 mmol, 1.0 equiv), and DCE (2 mL), under nitrogen. [b]Isolated yields.

With the enaminone scope probed, the oxadiazolone side is then scrutinized by reacting with **1a** (Scheme 5). The reaction can progress smoothly with **2a** phenyl *para*-

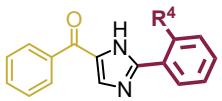
substituted, and the electronic property dictates the product yield: the electron-donating substitution (Me, **2b**, 70%; $^{i}$Pr, **2c**, 60%; OMe, **2d**, 58%) confers a higher yield than the electron-withdrawing one (F, **2e**, 36%; COOMe, **2f**, 34%;). For the *ortho* substitution, a similar trend holds, albeit with a diminished gap on yield (Me, **2g**, 67%; OMe, **2h**, 56%; F, **2i**, 45%; Cl, **2j**, 44%; Br, **2k**, 47%). For the *meta* substitution, the electron-donating one (Me, **2l**, 59%; OMe, **2m**, 51%) is lower in yield than the *para* and *ortho* counterparts, whereas the electron-withdrawing one (F, **2n**, 39%) is in between. The

**Scheme 5. Substrate Scope of Oxadiazolones from the Conventional Perspective.**[a][b]

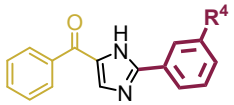


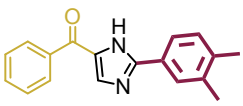
**3ab**: $R^4$ = Me, 70%
**3ac**: $R^4$ = $^{i}$Pr, 60%
**3ad**: $R^4$ = OMe, 58%
**3ae**: $R^4$ = F, 36%
**3af**: $R^4$ = COOMe, 34%



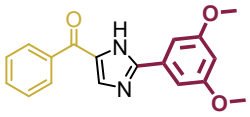
**3ag**: $R^4$ = Me, 67%
**3ah**: $R^4$ = OMe, 56%
**3ai**: $R^4$ = F, 45%
**3aj**: $R^4$ = Cl, 44%
**3ak**: $R^4$ = Br, 47%



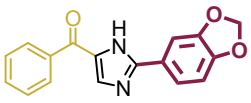
**3al**: $R^4$ = Me, 59%
**3am**: $R^4$ = OMe, 51%
**3an**: $R^4$ = F, 39%



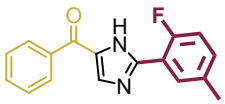
**3ao**: 57%



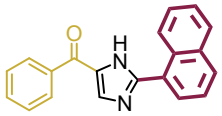
**3ap**: 53%



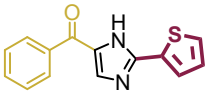
**3aq**: 46%



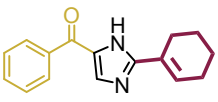
**3ar**: 71%



**3as**: 40%



**3at**: 43%



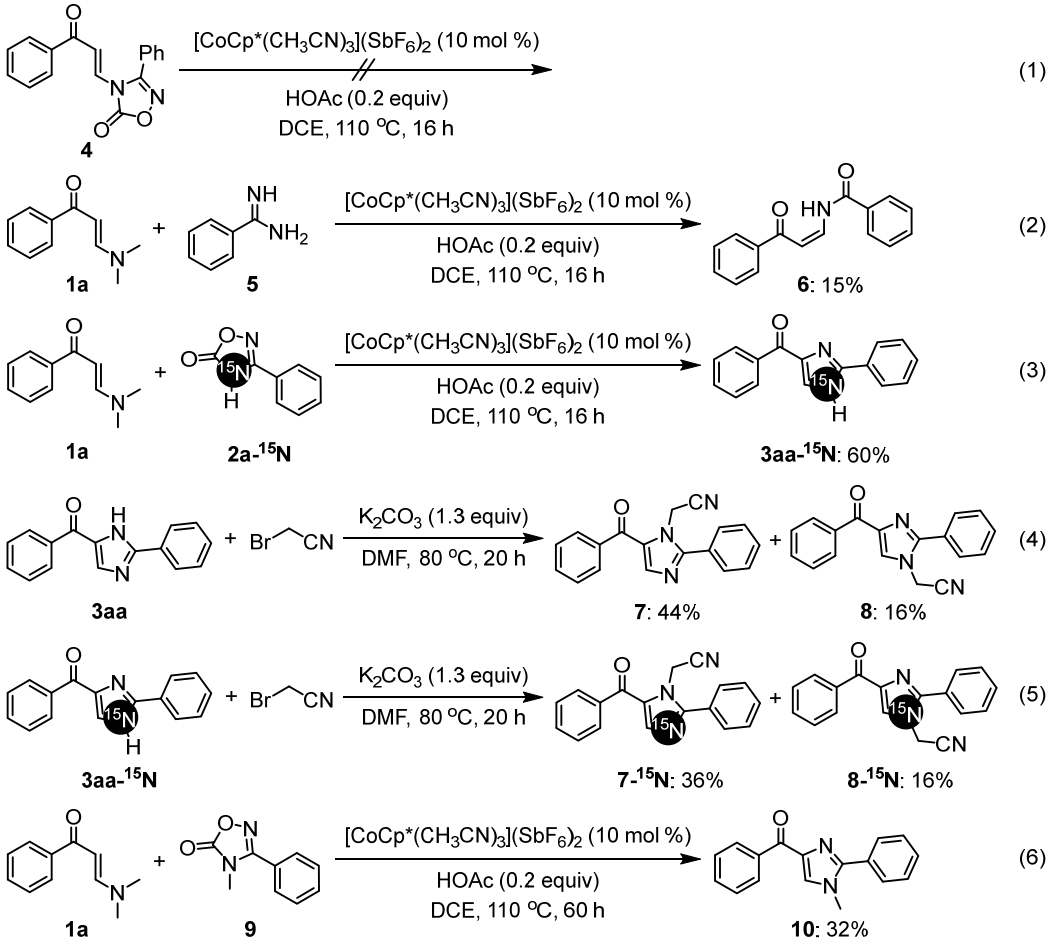
**3au**: 38%

[a]Reaction condition: compounds **1a** (0.24 mmol, 1.2 equiv), **2b** - **2u** (0.2 mmol, 1.0 equiv), and DCE (2 mL), under nitrogen. [b]Isolated yields.

reaction is permissive toward a disparate assortment of disubstitutions (**2o**, 57%; **2p**, 53%; **2q**, 46%; **2r**, 71%;). The replacement of **2a** phenyl with naphthalen-2-yl (**2s**, 40%), thiophen-2-yl (**2t**, 43%), and cyclohex-1-en-1-yl (**2u**, 38%) leads to a lower yield.

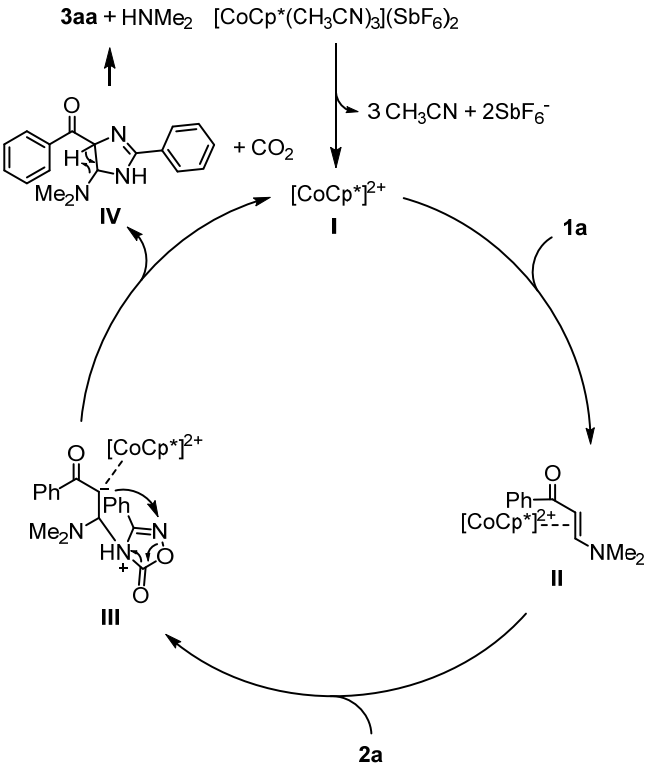
With the substrate scope interrogated, we next explore the reaction mechanism (Scheme 6). The reaction is not initiated by the nucleophilic substitution of enaminone amino group by oxadiazolone: the as-synthesized **4** (a hypothetical intermediate from **1a** and **2a**) shows no reactivity onward to **3aa** under otherwise optimized condition (eq. 1). The masked protection of amidine as oxadiazolone is critical for the reaction: **1a** and **5** only couple to an open-chain product **6** (15%; involving imine to carbonyl conversion) (eq. 2). The exclusive N1-C5/N3-C4 bonding is supported by two lines of

**Scheme 6. Mechanistic Studies.**



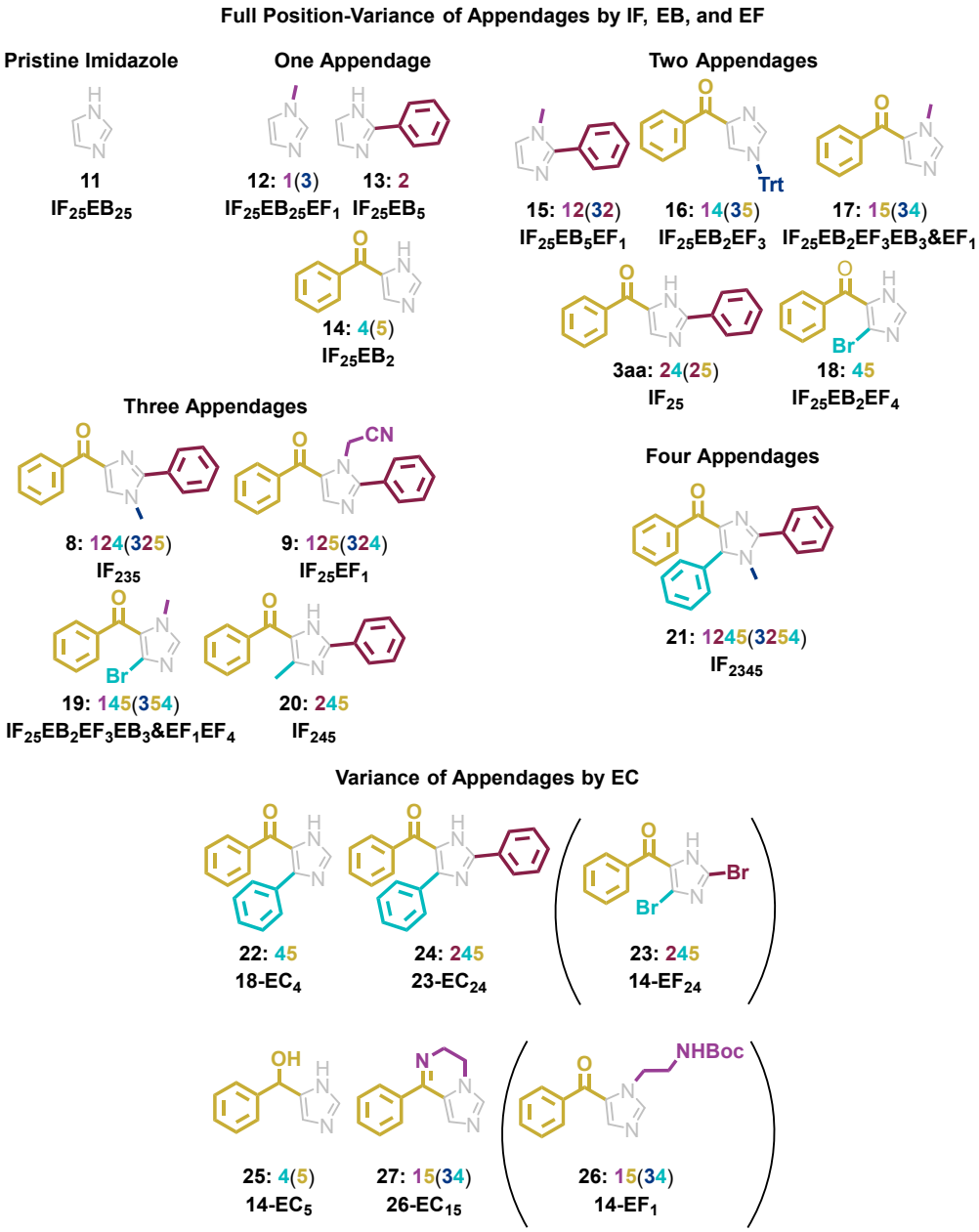
evidence: 1) a reaction between **1a** and $^{15}$N3-labeled **2a**, **2a-$^{15}$N**, offers only $^{15}$N3-labeled **3aa**, **3aa-$^{15}$N** (eq. 3) (the location of $^{15}$N is determined by the characterization of cyanomethyl derivatives of **3aa-$^{15}$N**: **7**, **8**, **7-$^{15}$N**, and **8-$^{15}$N**: eqs. 4 and 5); 2) a reaction between **1a** and N3-methylated **2a**, **9**, provides N3-methylated **3aa**, **10** (eq. 6). Taken together, a Co(III) Lewis acid catalytic mechanism is proposed as the following for an exemplary reaction between **1a** and **2a** (Scheme 7): binding and activation of **1a** by $[CoCp^*]^{2+}$ (**I**) to give **II**, nucleophilic attack of **II** C4 by **2a** N3 to afford **III**, nucleophilic cyclization attack of **III** N1 by C5 to form **IV**, together with the extrusion of $CO_2$ and release of **I**, deaminative aromatization of **IV** to produce **3aa**.

**Scheme 7. Proposed Catalytic Mechanism.**




With the conventional skeleton speciation-oriented synthesis accomplished, we next advance to the demonstration of appendage speciation-oriented synthesis, epitomized by the achievement of full position-variance of appendages (Scheme 8).

**Scheme 8. Appendage Speciation-Oriented Synthesis Achievement of Full Position-Variance of Appendages by IF, EB, and EF and Variance of Appendages by EC.**




The pristine imidazole (**11**) is synthesized by an $IF_{25}EB_{25}$ reaction sequence (herein, only an appendage undergoing both IF and EB reactions is explicitly noted, with the rest of the appendages self-evident on the organic species; 2: COOEt; 5: COOEt). The other proximal speciation stems from the following reaction sequences: one appendage: **12**, 1(3), $IF_{25}EB_{25}EF_1$ (2: COOEt; 5: COOEt); **13**, 2, $IF_{25}EB_5$ (5: COOEt); **14**, 4(5),

$IF_{25}EB_2$ (2: COOEt); two appendages: **15**, 12(32), $IF_{25}EB_5EF_1$ (5: COOEt); **16**, 14(35), $IF_{25}EB_2EF_3$ (2: COOEt; Trityl, or Trt); **17**, 15(34), $IF_{25}EB_2EF_3EB_3\&EF_1$ (2: COOEt; 3: Trt; &: simultaneous reactions); **3aa**, 24(25), $IF_{25}$; **18**, 45, $IF_{25}EB_2EF_4$ (5: COOEt); three appendages: **8**, 124(325), $IF_{235}$; **9**, 125(324), $IF_{25}EF_1$; **19**, 145(354), $IF_{25}EB_2EF_3EB_3\&EF_1EF_4$ (2: COOEt; 3: Trt); **20**, 245, $IF_{245}$; four appendages: **21**, 1245(3254), $IF_{2345}$. In addition, proximal speciation can also emanate from conversion of existing appendages (Scheme 8). For example, Br coupling conversion to phenyl on **18** furnishes **22** (45; **18**-$EC_4$); double Br coupling conversions to two phenyls on **23** (245; from **14**; **14**-$EF_{24}$) provides **24** (245; **23**-$EC_{24}$); carbonyl conversion to hydroxyl on **14** provides **25** (4(5); **14**-$EC_5$); conversions of carbonyl and amino to imine on **26** (15(34); from **14**; **14**-$EF_1$) affords **27** (15(34); **26**-$EC_{15}$).

In summary, we have demonstrated herein the concept of appendage speciation-oriented synthesis, emphasizing primary organic speciation by peripheral appendages, instead of skeleton. This synthetic modality seeks the maximization of type-, position-, and configuration-variance of appendages, in contrast to the conventional skeleton speciation-oriented synthesis. A Co(III) catalytic protocol in accord with this synthetic modality has been developed for coupling of enaminones and oxadiazolones to imidazoles, permitting the full synthetic coverage of position-variance of appendages through in situ and ex situ appendage speciation. This translates to expanded reaction and structural development scope and can provide a versatile synthetic handle for productive organic synthesis.

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