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Catalytic Aerobic Cross-Dehydrogenative Coupling of Azlactones en Route to α,α-Disubstituted α-Amino Acids

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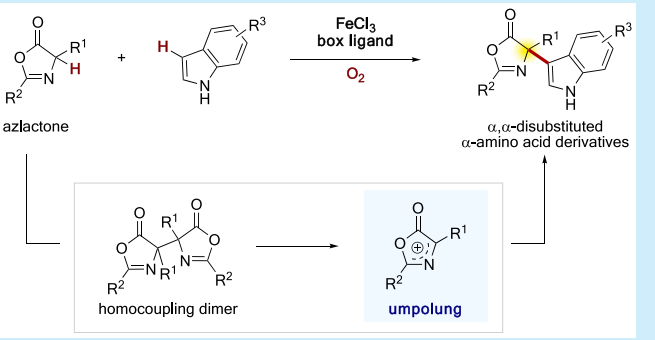
ABSTRACT: We developed a catalytic aerobic method to synthesize α,α-disubstituted α-amino acids through cross-dehydrogenative coupling of azlactones. Combining an iron catalyst with a bisoxazolidine ligand resulted in high catalytic performance, and cross-coupling with an indole proceeded smoothly under aerobic conditions. A wide variety of α-aryl and aliphatic amino acid derived azlactones were applied to the present catalysis. In addition, a quaternary carbon could be constructed using oxindole and benzofuranone under aerobic conditions.

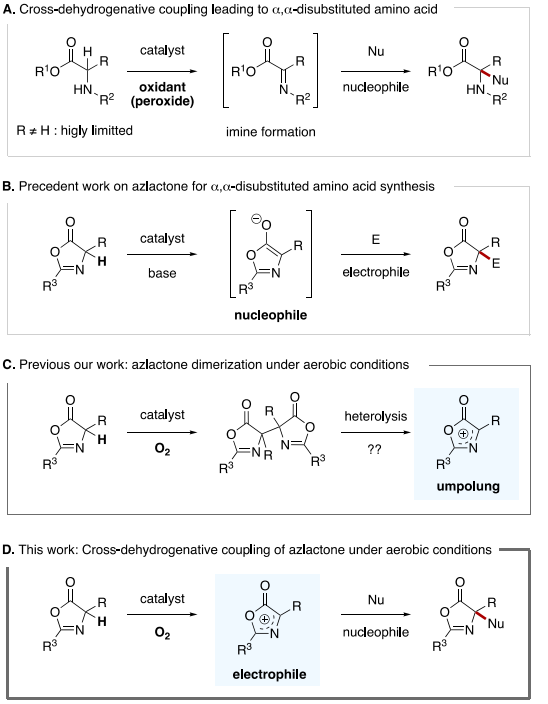


Unnatural α-amino acids are widely distributed in pharmaceuticals and functional materials, and are useful building blocks in synthetic organic chemistry and functional materials.[1] α,α-Disubstituted α-amino acids, which could increase chemical stability and fix peptide conformation, are attractive structural motifs for drug discovery.[2] Although many synthetic methods for unnatural α-amino acids are reported, the number of corresponding α,α-disubstituted α-amino acids reported is relatively small due to the steric bulkiness of the α-carbon. In addition, environmentally friendly and efficient methods are in high demand.

Cross-dehydrogenative coupling is a highly straightforward and environmentally friendly method for constructing a new carbon−carbon bond.[3] Cross-dehydrogenative coupling reactions toward unnatural α-amino acids, however, has been restricted to the glycine-derived imine formation followed by a nucleophilic addition reaction (Scheme 1A, R = H).[4] Among these reactions, a synthetic method for sterically congested α,α-disubstituted α-amino acids has remained unexplored and peroxide is usually required as a terminal oxidant for efficient reaction progress (Scheme 1A, R ≠ H).[5] Furthermore, the reaction must be carried out under high temperature conditions, which limits functional group compatibility. Oxygen is abundant and regarded as an ideal terminal oxidant. The difficulty in using oxygen is that the triplet state oxygen rapidly couples with α-amino acid precursors, especially α,α-disubstituted carbonyls, and generates undesired α-oxidation products. Therefore, no catalytic cross-dehydrogenative coupling reactions for α,α-disubstituted α-amino acids under aerobic conditions have yet been reported.

α-Amino acid derived azlactone has been widely utilized as a nucleophile for the synthesis of α,α-disubstituted α-amino acid

Scheme 1. α,α-Disubstituted Amino Acid Synthesis



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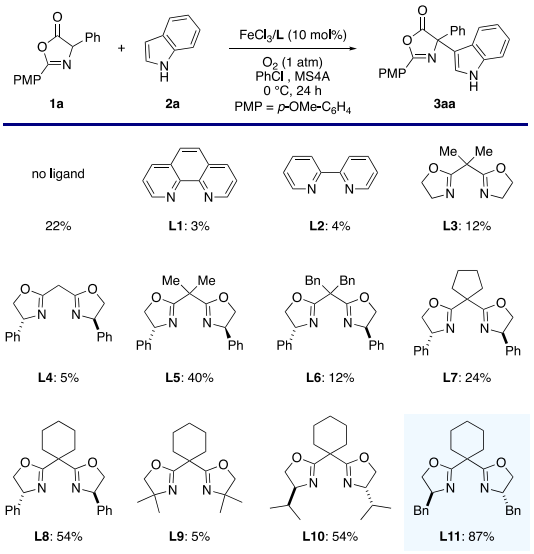
Scheme 2. Oxidative Cross-Enolate Coupling[a]

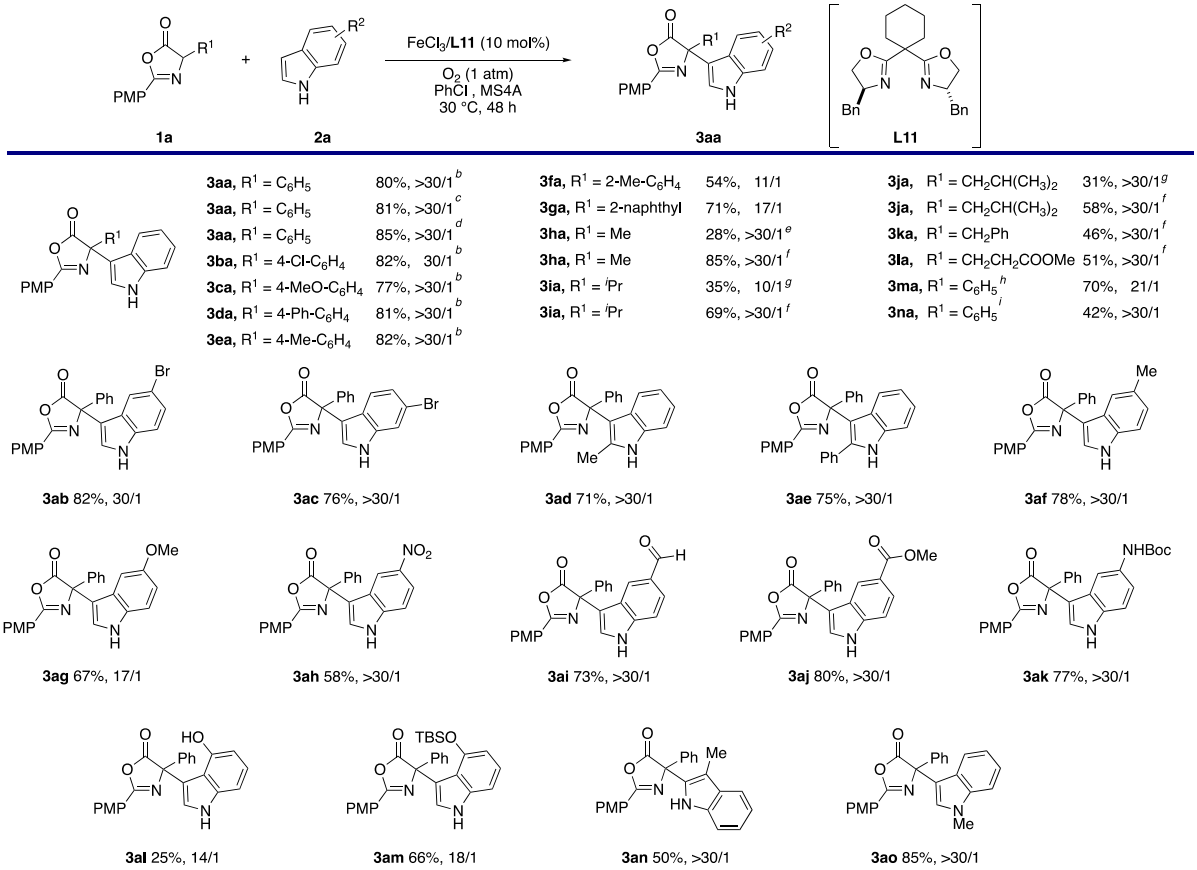


[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), PhCl (0.4 mL), MS4A (100 mg). NMR yields are shown.

(Scheme 1B).[6] We recently developed a tetrasubstituted carbon constructive oxidative cross-enolate coupling reaction using azlactone with peroxide as a terminal oxidant.[7] The reaction proceeded through a transient azlactone-derived homocoupling dimer, enabling a chemoselective cross-coupling reaction. In the course of this research, we observed that the azlactone rapidly underwent dimerization[8] when using an iron catalyst under aerobic conditions without forming an undesired α-oxidation product. Thus, we hypothesized that heterolysis of the formed homocoupling dimer would deliver highly electrophilic azaallyl cationic species (umpolung),[9] thereby overcoming the steric constraints (Scheme 1C). Herein we report iron-catalyzed cross-dehydrogenative coupling for the synthesis of α,α-disubstituted α-amino acids under aerobic conditions via the umpolung of azlactones (Scheme 1D). To the best of our knowledge, this is the first example of the synthesis α,α-disubstituted α-amino acids through cross-dehydrogenative coupling under aerobic conditions.

We began our study using azlactone **1a**, indole (**2a**), and $FeCl_3$ under an oxygen atmosphere as a terminal oxidant (Scheme 2).[10,11] Without any ligand, cross-coupling product **3aa** was produced in 22% yield. The addition of **L1** or **L2** decreased the chemical yield. The structure of the bisoxazolidine ligand highly affected the chemical yield.

Scheme 3. Substrate Generalities[a]



[a]Conditions: **1** (0.2 mmol), R^1 = Ar: **2** (0.3 mmol), R^1 = alkyl: **2** (0.4 mmol), PhCl (0.4 mL), MS4A (100 mg). Isolated yields are shown. Regioisomer ratio (rr) of C4/C2 of azlactone is shown. [b]Reaction was performed at 0 °C. [c]Air was used instead of oxygen. [d]Reaction was performed in 4.0 mmol scale. [e]Reaction was performed at 0 °C in 1,2-dichloroethane. [f]DTBP was used instead of oxygen in 1,2-dichloroethane at 70 °C. [g]Air was used instead of oxygen in 1,2-dichloroethane at 70 °C. [h]p-Me-C_6H_4 substituted azlactone **1m** was used instead of PMP substituted **1a**. [i]p-Br-C_6H_4 substituted azlactone **1n** was used instead of PMP substituted **1a**.

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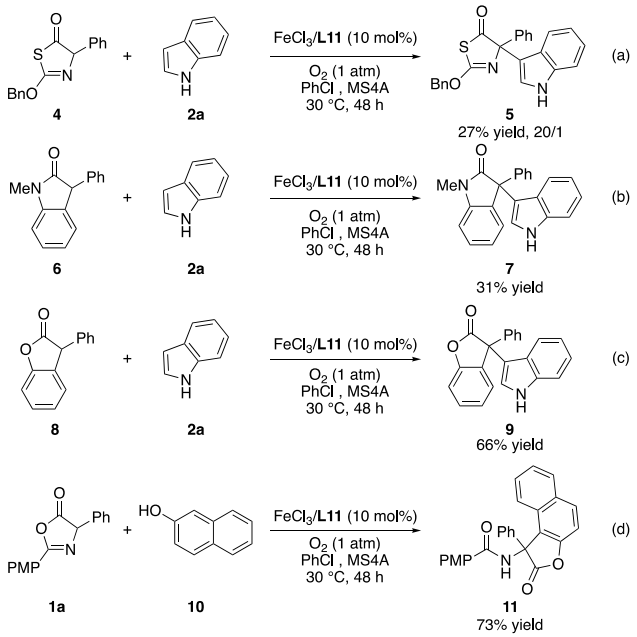
Scheme 4. Further Substrate Scope[a]



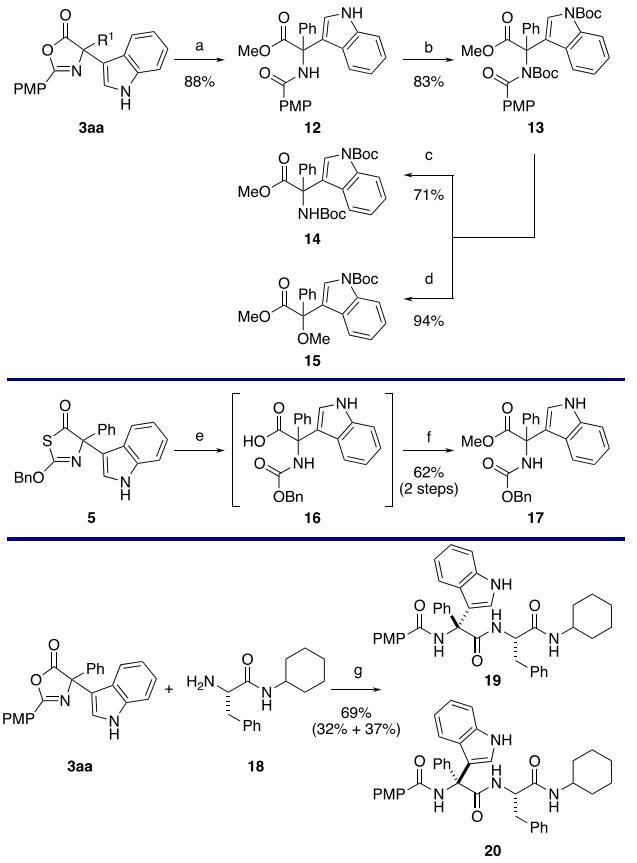
[a]Conditions: **1** (0.2 mmol), **2** (0.3 mmol), PhCl (0.4 mL), MS4A (100 mg). Isolated yields are shown. Regioisomer ratio (rr) of C4/C2 of **5** is shown.

Although **L3** and **L4** exhibited poor catalytic performance, ligand **L5** had higher catalytic activity and provided the product in 40% yield. The ring size of the bisoxazolidine ligand was important to produce a high chemical yield (**L7**, **L8**).[12] The bisoxazolidine ligand bearing a six-membered ring **L8** exhibited higher catalytic performance than the corresponding five-membered ring **L7**. A survey of substituents at the 4-position revealed that a dibenzyl-substituted bisoxazolidine ligand was optimal and the product was observed in 87% yield (**L11**).[13,14]

Under the identical conditions, we determined the substrate scope, as shown in Scheme 3. The reaction could be performed under an air atmosphere, and product **3aa** was isolated in 81% yield. Large-scale reactions had no detrimental effects on the yield. A variety of phenyl glycine derivatives were applicable under optimized or slightly modified reaction conditions (**3ab**−**3ga**). Neither electron-donating nor electron-deficient substituents had a detrimental effect (**3ab**−**3ea**). A sterically hindered 2-methyl substituent exhibited moderate reactivity and provided product **3fa** in 54% yield. The 2-napththyl substrate also afforded product **3ga** in high yield. Aliphatic amino acid derived azlactones, alanine, valine, and leucine were also applicable under slightly modified reaction conditions, although the yields were moderate (**3ha**−**3ja**). The use of di-*tert*-butylperoxide instead of oxygen as an oxidant provided the products in higher yield (**3ha**−**3la**). The substituent at the C2 position of azlactone could be changed to *p*-Me-C_6H_4 or *p*-Br-C_6H_4 respectively, although the chemical yields were slightly decreased (**3ma**, **3na**).

We next performed the reaction using various indoles **2**. A bromo substituent at the 5- or 6-positions did not affect the chemical yields (**3ab**, **3ac**). The 2-substituted indoles provided highly congested α,α-diaryl α-amino acid products in high yield (**3ad**, **3ae**). Various substituents, an alkyl group, methoxy, nitro, formyl, ester, and protected amino group, were tolerated

Scheme 5. Transformation of the Products Conditions[a]



[a](a) (+)-CSA (10 mol %), CH_2Cl_2, rt, 24 h, 88%. (b) DMAP (20 mol %), Boc_2O, 1.4-dioxane, 80 °C, 48 h, 83%. (c) $NH_2NH_2{\cdot}H_2O$, THF/MeOH, 70 °C, 24 h, 71%. (d) Cs_2CO_3, MeOH, rt, 24 h, 94%. (e) LiOH, H_2O_2, THF/H_2O, rt, 10 h. (f)TMSCHN$_2$, toluene/MeOH, rt, 1 h, 62% (2 steps). (g) NMP, 70 °C, 24 h, 32% + 37%.

under the optimized conditions (**3af**−**3ak**). Although an indole bearing a protecting-group-free hydroxy group exhibited low reactivity, a TBS-protected hydroxy group provided the product in high yield (**3al**, **3am**). When 3-methyl substituted indole was used, the reaction proceeded at the 2-position, providing product **3an** in high yield. An *N*-methyl indole was also applicable (**3ao**).

The efficiency of the present aerobic catalysis was demonstrated by further screening the substrate scope using various coupling partners instead of azlactone (Scheme 4). 2-Benzyloxythiazol-5(4*H*)-ones, which could be easily transformed into Cbz-protected amino acid derivatives (vide infra),[15] provided the product in 27% yield (Scheme 4a). Oxindole and benzofuranone were also applicable to the present catalysis, allowing for the construction of a quaternary carbon center (Scheme 4b, c).[16,17] When 2-naphthol was used instead of indole, product **11** was isolated in high yield through cross-dehydrogenative coupling followed by intramolecular ring opening of azlactone (Scheme 4d).

The synthetic utility of the product through catalytic aerobic cross-dehydrogenative coupling was demonstrated by further transformation (Scheme 5). Ring opening of azlactone by methanol proceeded under acidic conditions followed by Boc protection of two amino groups, delivering product **13** in high yield. Chemoselective hydrazinolysis of imide over methyl ester was achieved to afford the Boc-protected α,α

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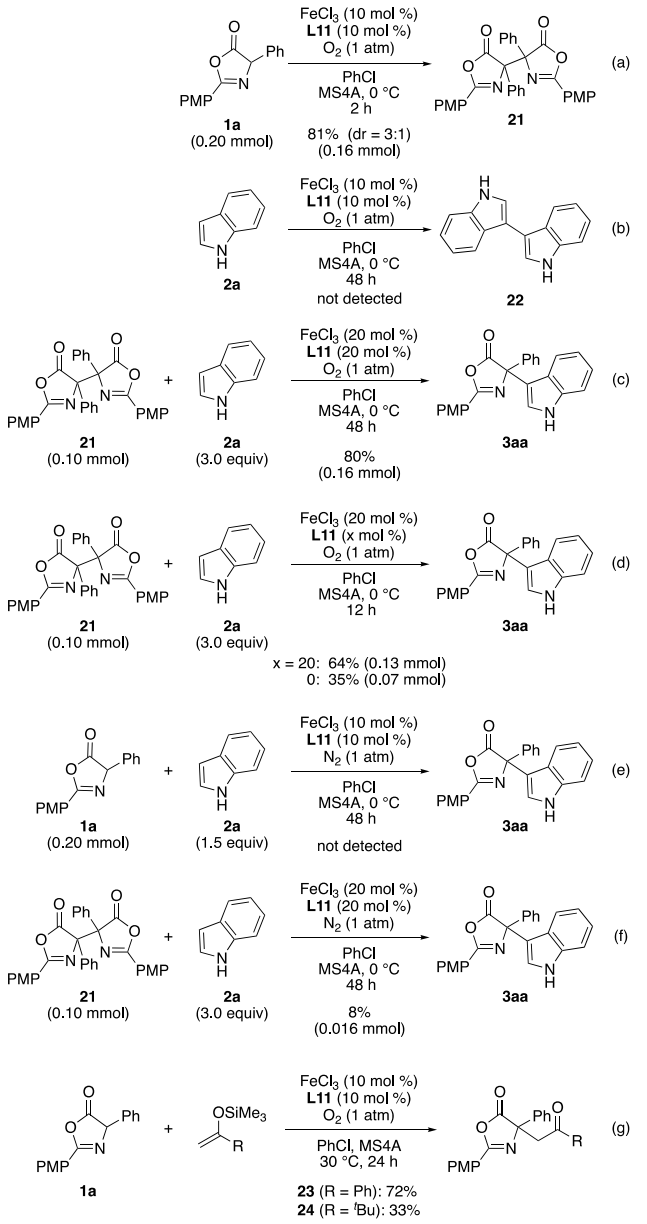
Scheme 6. Series of Control Experiments



-disubstituted amino acid derivative **14**. Treatment of cesium carbonate in methanol underwent α-substitution, providing α,α-disubstituted hydroxy acid derivative **15** in high yield. 2-Benzyloxythiazol-5(4*H*)-one-derived product **5** was easily converted into readily removable Cbz-protected α,α-disubstituted amino ester **17**, demonstrating that the present catalysis is highly useful for synthesizing α,α-disubstituted amino or hydroxy acid derivatives. The synthesized racemic **3aa** was easily separated into an enantiopure form after an amidation reaction with chiral phenylalanine amide by conventional column chromatography.[18,19]

We next performed several control experiments (Scheme 6). Homocoupling dimer **21** was observed in high yield in the absence of indole (**2a**) (Scheme 6a). This dimerization process would have a sufficient reaction rate to avoid an undesired α-oxidation reaction induced by oxygen. In contrast, no homocoupling dimer derived from indole **22** was observed (Scheme 6b). When homocoupling dimer **21** was subjected to the standard reaction conditions instead of azlactone **1a**, product **3aa** was observed in high yield, indicating that homocoupling dimer **21** would be an active intermediate (Scheme 6c). The ligand was found to facilitate the cross-coupling of homocoupling dimer **21** with indole (**2a**), presumably through the generation of ion paired catalyst $[FeL_nCl_2]^+[FeCl_4]^-$ (Scheme 6d).[20] Only low chemical yields were observed under a nitrogen atmosphere using **1a** or homocoupling dimer **21** as the starting material (Scheme 6e and 6f). We also confirmed the generation of azlactone-derived azaallyl cationic species (ionic pathway) using silyl enol ethers (Scheme 6g).[21] The cross-couplings with silyl enol ethers proceeded under optimized reaction conditions to afford the products **23** and **24**, supporting the generation of azaallyl cationic species. These results also verified that the present catalytic aerobic cross-dehydrogenative coupling could use a variety of nucleophilic coupling partners instead of indoles.

The postulated catalytic cycle based on mechanistic studies is depicted in Figure 1. First, actual catalytic species **I** would be generated by **L11**. The enolization of azlactone would be achieved by catalytic species **I** to afford enolate **II**. Dimerization would proceed via the resonance radical species **III**, delivering the homocoupling dimer **21** with the generation of iron(II) species. The iron(II) species would be oxidized by oxygen to regenerate catalytic species **I**. Heterolytic cleavage of the formed homocoupling dimer **21** by catalytic species **I**

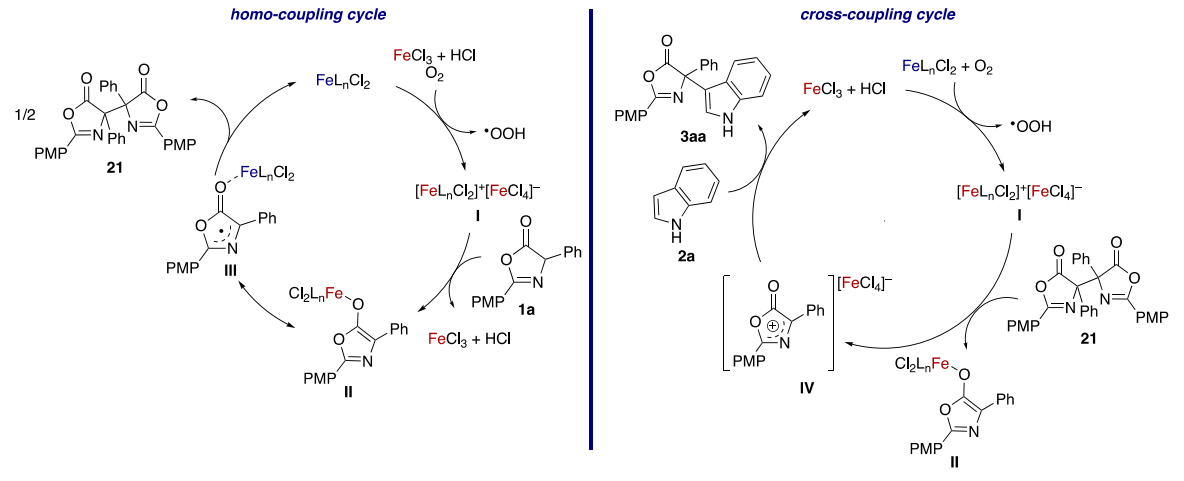


Figure 1. Postulated catalytic cycle.

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would provide highly reactive cationic species **IV** with the concomitant formation of iron(II) species. A nucleophilic attack of indole would proceed to afford the product with the concomitant formation of $FeCl_3$ and hydrogen chloride. Finally, the regeneration of catalytic species **I** would be achieved by oxygen.

In conclusion, we developed a catalytic aerobic cross-dehydrogenative coupling reaction of azlactones leading to α,α-disubstituted α-amino acids. The reaction proceeded under very mild conditions, 30 °C without bases, and with wide functional group compatibility. To the best of our knowledge, this is the first example of the synthesis of α,α-disubstituted α-amino acids through cross-dehydrogenative coupling under aerobic conditions. Further studies to expand the application of the present aerobic cross-dehydrogenative coupling are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01248.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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