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Enantioselective Syntheses of C_2-Symmetric Pyrazolones and Diones via One-Pot Organo-/Iodine Sequential Catalysis

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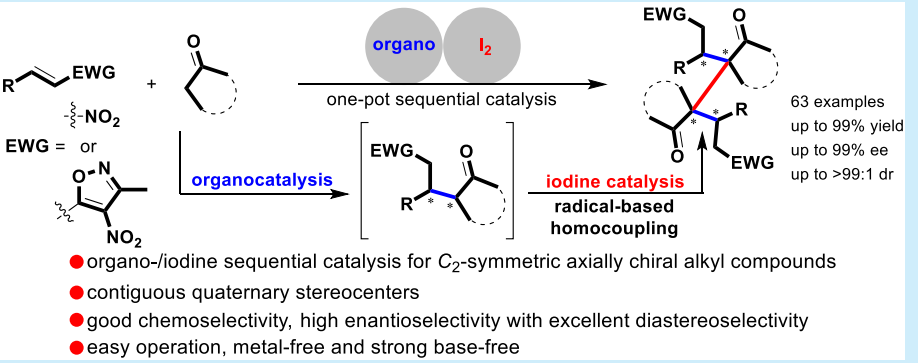

ABSTRACT: The catalytic diastereo- and enantioselective syntheses of C_2-symmetric axially chiral 1,4-dicarbonyl derivatives with 2,3-quaternary stereocenters were achieved by utilizing an organo-/iodine binary catalytic strategy. The reactions proceeded well under mild conditions without metals or strong bases.

C_2-symmetric axially chiral frameworks constitute important structural motifs in a number of natural products and biologically active molecules.[1] Moreover, they act as core scaffolds in many privileged organocatalysts and ligands.[2] Many efforts have been devoted to the enantio- and diastereoselective synthesis of C_2-symmetric axially chiral biaryl backbones because of the wide range of applications of these motifs, and numerous novel and practical routes have been established.[2,3] However, to the best of our knowledge, the catalytic enantio- and diastereoselective construction of the C_2-symmetric axially chiral alkyl skeleton with contiguous quaternary stereocenters is more challenging and considerably less explored than that of well-developed C_2-symmetric axially chiral biaryl architectures, likely due to the relatively low atropisomerization barrier around the C_2-symmetric axis (Scheme 1, a).

1,4-Dicarbonyl molecules are found in a wide range of biologically active compounds,[4] and their synthetic utility has been effectively demonstrated.[5] Consequently, the enantio- and diastereoselective syntheses of 1,4-dicarbonyl moieties have attracted considerable attention.[6] However, methods for the catalytic asymmetric construction of C_2-symmetric axially chiral 1,4-dicarbonyl derivatives remain underdeveloped.[7] Current chiral construction strategies include (1) the indirect single-electron transfer (SET) oxidative coupling of preformed chiral enolates, a process that generally needs a strong base and a metal oxidant but exhibits only moderate diastereoselectivities;[5b,8] (2) the direct asymmetric organocatalytic oxidative homocoupling of aldehydes with a metal oxidant;[9] (3) the direct asymmetric homodialkylation of bisoxindoles with a base;[10] and (4) the metal-catalyzed double Michael addition.[5c,11] For example, in 2011, Thomson's group developed a process for the efficient $CuCl_2$-promoted oxidative coupling of preformed chiral lithium enolates to construct enantioselective C_2-symmetric 1,4-diketones (Scheme 1, b1).[5b] In 2018, Jørgensen and co-workers presented a novel methodology for the direct organocatalytic stereoselective oxidative homocoupling of α-substituted aldehydes via open-shell intermediates with Ag_2CO_3 as an oxidant to construct chiral C_2-symmetric 1,4-dialdehydes (Scheme 1, b2).[9] However, the reported cases suffered from the multistep preparation of chiral starting substrates, low diastereoselectivity and/or enantioselectivity, narrow substrate scope, and requirement of stoichiometric amounts of strong bases and metal oxidants. Therefore, developing general and effective catalytic

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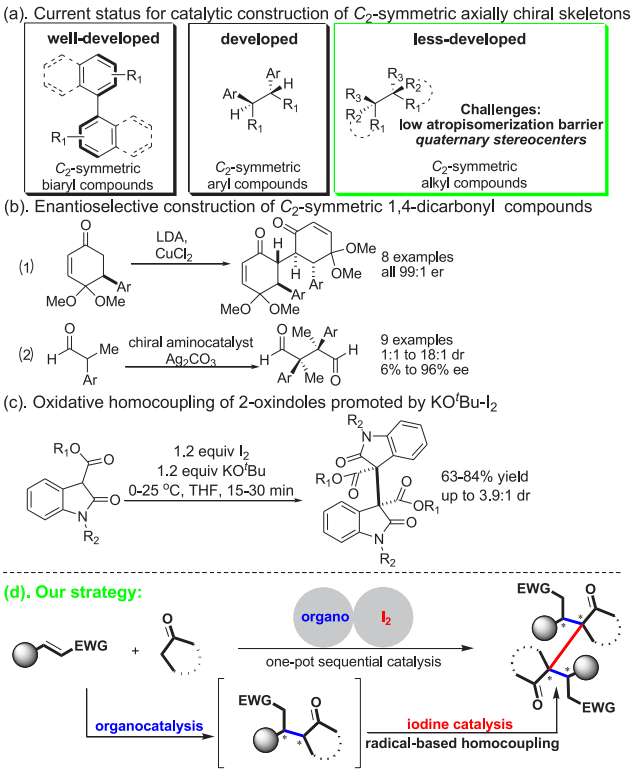
Scheme 1. Design of Organo-/Iodine Sequential Catalysis for C_2-Symmetric Axially Chiral Compounds

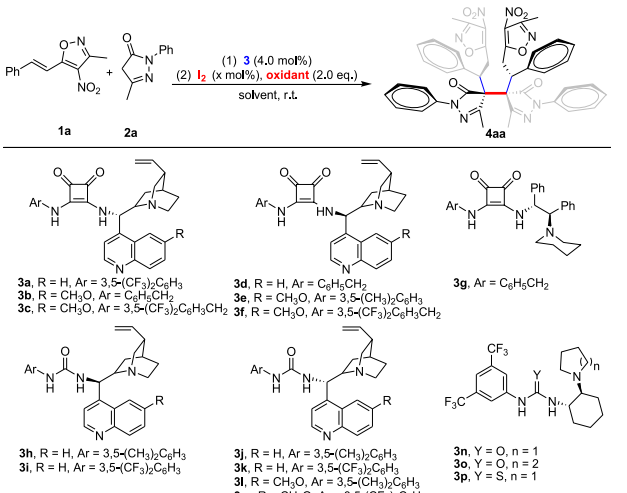


methods to construct novel C_2-symmetric axially chiral alkyl derivatives is interesting and urgent.

Previous works have demonstrated that iodine is not only a "metal-like" compound with mild Lewis acid characteristics but also an efficient radical donor, and iodide can be oxidized to molecular iodine.[12] On the basis of those concepts, our group developed an innovative organo-/iodine binary catalyst system to synthesize structurally and stereochemically diverse spiro compounds.[13] In 2015, Bisai and co-workers developed a novel KO^{t}Bu- and I_2-promoted protocol to synthesize a structurally diverse range of racemic dimeric 2-oxindoles with low diastereoselectivities via SET oxidation and the radical-based homocoupling pathway (Scheme 1, c).[7c] Inspired by the above works and as a part of our ongoing research projects on applications of organo/iodine binary catalytic strategies in asymmetric catalysis, herein, we report the first efficient method for the construction of C_2-symmetric axially chiral pyrazolones and diones via chiral hydrogen bonding and molecular iodine sequential catalysis without transition metals and strong bases (Scheme 1, d).

The designed sequential catalytic reaction of isoxazole nitroolefin **1a** and pyrazolone **2a** was initially examined in the presence of the chiral hydrogen bonding catalyst **3a**, molecular iodine, H_2O_2, and CH_2Cl_2 (Table S0).[14] The desired product **4aa** was selectively obtained with 70% yield, 76% ee, and >99:1 dr (Table 1, entry 1). Given this encouraging result, a series of squaramide, urea, and thiourea catalysts were next tested (entries 2−16). Evidence from the screening of the squaramide catalysts **3b**−**3g** (entries 2−7) showed that squaramide architectures provided 35% to 99% yield, 25% to −83% ee, and all >99:1 dr. Urea catalysts gave 76%−99% yields and 62%−90% enantiomeric excesses with excellent diastereoselectivities (entries 8−15). The best results

Table 1. Screening of Reaction Conditions[a]



entry	cat.	oxidant	solvent	yield[b] (%)	ee[c] (%)	dr[d]
1	**3a**	H_2O_2	CH_2Cl_2	70	76	>99:1
2	**3b**	H_2O_2	CH_2Cl_2	75	66	>99:1
3	**3c**	H_2O_2	CH_2Cl_2	55	75	>99:1
4	**3d**	H_2O_2	CH_2Cl_2	91	−61	>99:1
5	**3e**	H_2O_2	CH_2Cl_2	75	−66	>99:1
6	**3f**	H_2O_2	CH_2Cl_2	99	−83	>99:1
7	**3g**	H_2O_2	CH_2Cl_2	35	25	>99:1
8	**3h**	H_2O_2	CH_2Cl_2	76	−66	>99:1
9	**3i**	H_2O_2	CH_2Cl_2	78	−82	>99:1
10	**3j**	H_2O_2	CH_2Cl_2	88	72	>99:1
11	**3k**	H_2O_2	CH_2Cl_2	98	85	>99:1
12	**3l**	H_2O_2	CH_2Cl_2	85	62	>99:1
13	**3m**	H_2O_2	CH_2Cl_2	90	84	>99:1
14	**3n**	H_2O_2	CH_2Cl_2	99	90	>99:1
15	**3o**	H_2O_2	CH_2Cl_2	95	85	>99:1
16	**3p**	H_2O_2	CH_2Cl_2	75	85	>99:1
17[e]	**3n**	H_2O_2	CH_2Cl_2	96	90	>99:1
18[f]	**3n**	**H_2O_2**	**CH_2Cl_2**	**95**	**92**	**>99:1**
19[g]	**3n**	H_2O_2	CH_2Cl_2	63	90	>99:1
20[h]	**3n**	H_2O_2	CH_2Cl_2	30	88	>99:1

[a]Reaction conditions: **1a** (0.24 mmol, 1.2 equiv), **2a** (0.2 mmol), and organocatalyst **3** (4.0 mol %) in solvent (2.0 mL), r.t., 48 h; then I_2 (0.1 mmol, 50 mol %), H_2O_2 (2.0 equiv, 30% aqueous), r.t., 3 min. [b]Isolated yield. [c]Enantiomeric excess was determined through HPLC analysis by using a Chiralcel IC-H. [d]dr was determined through ^{1}H NMR analysis. [e]I_2 (40 mol %). [f]I_2 (30 mol %). [g]I_2 (20 mol %). [h]I_2 (10 mol %).

were achieved when the catalyst **3n**, which delivered **4aa** in 99% yield, >99:1 dr, and 90% ee (entry 14), was used. The thiourea catalyst **3p** was further screened and still provided **4aa** with 75% yield, 85% ee, and >99:1 dr (entry 16). Finally, iodine loadings of 40 mol % to 10 mol % were screened (entries 17−20). The iodine loading of 30 mol % was the better choice and gave **4aa** in 95% yield with 92% ee and >99:1 dr (entry 18).

With the optimized reaction conditions in hand, the scope of isoxazole nitroolefins **1** and pyrazolones **2** was investigated (Scheme 2). Different groups substituting for isoxazole nitroolefins **1** were first examined and provided **4aa**−**4ar** in moderate to high yields (70%−95%) with high to excellent enantioselectivities (84%−96% ee) and excellent diastereoselectivities (>99:1 dr). Electron-rich (MeO and Me) groups

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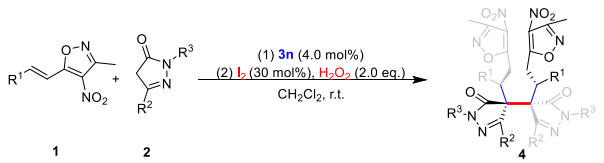
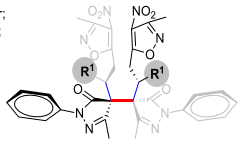
Scheme 2. Substrate Scopes for Isoxazole Nitroolefins and Pyrazolones[a]

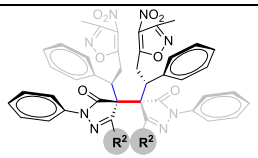


1 2 4

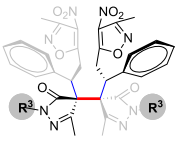
4aa: R^1 = C_6H_5, 95% yield, 92% ee, >99:1 dr;
4ab: R^1 = 3-$MeOC_6H_4$, 71% yield, 92% ee, >99:1 dr;
4ac: R^1 = 4-$MeOC_6H_4$, 70% yield, 90% ee, >99:1 dr;
4ad: R^1 = 2-MeC_6H_4, 79% yield, 92% ee, >99:1 dr;
4ae: R^1 = 3-MeC_6H_4, 79% yield, 90% ee, >99:1 dr;
4af: R^1 = 4-MeC_6H_4, 70% yield, 90% ee, >99:1 dr;
4ag: R^1 = 2-FC_6H_4, 80% yield, 92% ee, >99:1 dr;
4ah: R^1 = 3-FC_6H_4, 76% yield, 90% ee, >99:1 dr;
4ai: R^1 = 4-FC_6H_4, 72% yield, 94% ee, >99:1 dr;



4aj: R^1 = 2-ClC_6H_4, 79% yield, 84% ee, >99:1 dr;
4ak: R^1 = 3-ClC_6H_4, 79% yield, 92% ee, >99:1 dr;
4al: R^1 = 4-ClC_6H_4, 76% yield, 91% ee, >99:1 dr;
4am: R^1 = 3-BrC_6H_4, 74% yield, 94% ee, >99:1 dr;
4an: R^1 = 4-BrC_6H_4, 73% yield, 92% ee, >99:1 dr;
4ao: R^1 = 4-$NO_2C_6H_4$, 73% yield, 91% ee, >99:1 dr;
4ap: R^1 = 1-naphthyl, 74% yield, 96% ee, >99:1 dr;
4aq: R^1 = 2-thienyl, 83% yield, 87% ee, >99:1 dr;
4ar: R^1 = Pr, 78% yield, 88% ee, 99:1 dr;



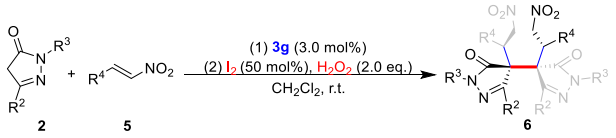
4ba: R^2 = Et, 82% yield, 90% ee, >99:1 dr;
4bb: R^2 = Pr, 79% yield, 92% ee, >99:1 dr;
4bc: R^2 = *i*-Pr, 72% yield, 91% ee, >99:1 dr;
4bd: R^2 = cyclopropyl, 98% yield, 90% ee, >99:1 dr;



4ca: R^3 = 2-MeC_6H_4, 80% yield, 97% ee, >99:1 dr;
4cb: R^3 = 3-ClC_6H_4, 87% yield, 99% ee, >99:1 dr;
4cc: R^3 = 3-BrC_6H_4, 79% yield, 98% ee, >99:1 dr;

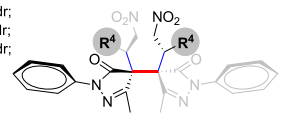
[a]Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), and organocatalyst **3n** (4.0 mol %) in CH_2Cl_2 (2.0 mL), r.t., 48 h; then I_2 (0.06 mmol, 30 mol %), H_2O_2 (2.0 equiv, 30% aqueous), r.t., 3 min.

Scheme 3. Substrate Scopes for Nitroolefins and Pyrazolones[a]

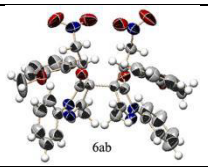


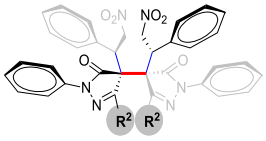
2 5 6

6aa: R^4 = C_6H_5, 84% yield, 97% ee, >99:1 dr;
6ab: R^4 = 2-$MeOC_6H_4$, 95% yield, 97% ee, >99:1 dr;
6ac: R^4 = 3-$MeOC_6H_4$, 86% yield, 95% ee, >99:1 dr;
6ad: R^4 = 4-$MeOC_6H_4$, 88% yield, 92% ee, >99:1 dr;
6ae: R^4 = 2-MeC_6H_4, 92% yield, 96% ee, >99:1 dr;
6af: R^4 = 4-MeC_6H_4, 94% yield, 99% ee, >99:1 dr;
6ag: R^4 = 4-FC_6H_4, 72% yield, 97% ee, >99:1 dr;
6ah: R^4 = 2-ClC_6H_4, 77% yield, 97% ee, >99:1 dr;

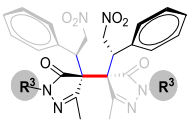


6ai: R^4 = 3-ClC_6H_4, 72% yield, 94% ee, >99:1 dr;
6aj: R^4 = 4-ClC_6H_4, 76% yield, 96% ee, >99:1 dr;
6ak: R^4 = 2-BrC_6H_4, 78% yield, 96% ee, >99:1 dr;
6al: R^4 = 4-BrC_6H_4, 74% yield, 95% ee, >99:1 dr;
6am: R^4 = 2,4-$Cl_2C_6H_3$, 62% yield, 97% ee, >99:1 dr;
6an: R^4 = 2-naphthyl, 79% yield, 98% ee, >99:1 dr;
6ao: R^4 = 2-furyl, 86% yield, 97% ee, >99:1 dr;
6ap: R^4 = 2-thienyl, 90% yield, 95% ee, >99:1 dr;





6ba: R^2 = Et, 93% yield, 94% ee, >99:1 dr;
6bb: R^2 = Pr, 96% yield, 92% ee, >99:1 dr;
6bc: R^2 = *i*-Pr, 87% yield, 95% ee, >99:1 dr;
6bd: R^2 = C_6H_5, 90% yield, 95% ee, >99:1 dr;
6be: R^2 = 4-$MeOC_6H_4$, 93% yield, 95% ee, >99:1 dr;
6bf: R^2 = 4-FC_6H_4, 88% yield, 95% ee, >99:1 dr;
6bg: R^2 = 4-BrC_6H_4, 80% yield, 95% ee, >99:1 dr;



6ca: R^3 = 2-MeC_6H_4, 80% yield, 98% ee, >99:1 dr;
6cb: R^3 = 2-FC_6H_4, 97% yield, 97% ee, >99:1 dr;
6cc: R^3 = 2-ClC_6H_4, 87% yield, 96% ee, >99:1 dr;
6cd: R^3 = 3-ClC_6H_4, 87% yield, 92% ee, >99:1 dr;
6ce: R^3 = 3-BrC_6H_4, 79% yield, 87% ee, >99:1 dr;
6cf: R^3 = 2-$NO_2C_6H_4$, 92% yield, 86% ee, >99:1 dr;
6cg: R^3 = *i*-Pr, 84% yield, 80% ee, >99:1 dr;

[a]Reaction conditions: **2** (0.2 mmol), **5** (0.24 mmol), and organocatalyst **3g** (3.0 mol %) in CH_2Cl_2 (2.0 mL), r.t., 6 h; then I_2 (50 mol %), H_2O_2 (2.0 equiv, 30% aqueous), r.t., 3 min.

(**1b**−**1f**) and electron-poor (F, Cl, Br, and NO_2) groups (**1g**−**1o**) on the phenyl group were well tolerated. Additionally, the naphthyl-substituted isoxazole nitroolefin **1p** and the heteroatom-substituted isoxazole nitroolefin **1q** underwent the sequential catalytic reaction to produce the desired products **4ap** and **4aq** in good yields (74% and 83%) with high enantioselectivities (96% and 87% ee) and excellent diastereoselectivities (>99:1 dr). Notably, in the case of the aliphatic isoxazole nitroolefin **1r**, the sequence also proceeded smoothly to present **4ar** in 78% yield with 88% ee and 99:1 dr. Next, the generality of pyrazolones was studied. A variety of substituent groups, such as Me, Et, Pr, and *i*-Pr groups, were tolerated well at the 5-position of pyrazolones, and when the steric hindrance of substituents increased, the yields of **4aa** and **4ba**−**4bc** decreased slightly but still presented 90%−92% ee and >99:1 dr. Remarkably, the cyclopropyl-bearing pyrazolone was converted into **4bd** with 98% yield, 90% ee, and >99:1 dr. Moreover, aromatic groups carrying pyrazolones at the 2-position showed good compatibility with the organo-/iodine sequential catalytic system to give products **4ca**−**4cc** with 80%−87% yields, 97%−99% ee, and >99:1 dr. On the scale of 2.0 mmol, the desired product **4aa** was achieved in 95% yield, with >99:1 dr and 90% ee.[14]

The reactions of pyrazolones **2** and nitroolefins **5** were further studied to evaluate the one-pot organo-/iodine sequential catalytic system well. Having identified the best reaction conditions (Table S1),[14] the scope of various nitroolefins **5** was investigated (Scheme 3). This asymmetric reaction advanced smoothly to give the desired products **6**. The substrates (**5a**−**5l**) with electron-donating and electron-withdrawing functional groups on the phenyl were well tolerated. The desired products **6aa**−**6al** were achieved with 72%−95% yields, 92%−99% ee, and >99:1 dr. The disubstituted aromatic ring substrate could furnish **6am** with 62% yield, 92% ee, and >99:1 dr. Notably, the reactions of **2a** with 2-naphthyl-, 2-furyl-, and 2-thienyl-substituted nitroolefins offered **6an**−**6ap** in 79%−95% yields with 95%−98% ee and >99:1 dr. The stereochemistry of **6ab** was assigned to (2*S*, 11*R*, 21*S*, 30*R*) by using X-ray crystallographic analysis.[14] Then, the generality of pyrazolones **2** was further investigated. The reaction proceeded efficiently with alkyl substituents (Me, Et, Pr, and *i*-Pr) on the 5-position of pyrazolones, providing

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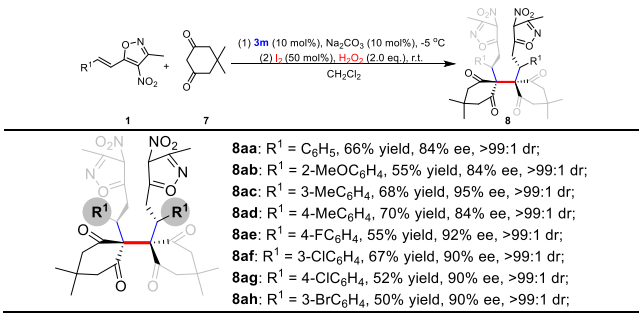
corresponding products **6** with high yields (87%−96%) and excellent stereoselectivities (92%−95% ee, all >99:1 dr, **6ba**−**6bc**). Aryl substituents, such as Ph, 4-MeOC_6H_4, 4-FC_6H_4, and 4-BrC_6H_4, were tolerated at the 5-position of pyrazolones to furnish **6bd**−**6bg** with 80%−93% yields and excellent stereoselectivities (95% ee, >99:1 dr). Next, a representative range of pyrazol-5-ones with diverse substituents (Me, F, Cl, Br, and NO_2) on the *N*-aryl group were tested and afforded products **6ca**−**6cf** in 79%−97% yields with 86%−98% ee and >99:1 dr. Moreover, the aliphatic *i*-Pr-substituted pyrazol-5-one provided **6cg** in 84% yield with 80% ee and >99:1 dr.

Encouraged by the obtained results, the performance of the highly challenging dicarbonyl compound 1,3-cyclohexanedione was further investigated (Scheme 4). Delightedly, under the optimized reaction conditions (Table S2),[14] all reactions smoothly delivered the corresponding products **8aa**−**8ah** in 50%−70% yields with 84%−95% ee and >99:1 dr.

Scheme 4. Substrate Scopes for Isoxazole Nitroolefins and 1, 3-Cyclohexanedione[a]



[a]Reaction conditions: **1** (0.45 mmol), **7** (0.3 mmol), organocatalyst **3m** (10.0 mol %), and Na_2CO_3 (10.0 mol %) in CH_2Cl_2 (2.0 mL), −5 °C, 48 h; then I_2 (50 mol %), H_2O_2 (2.0 equiv, 30% aqueous), r.t., 3 min.

A proposed sequential catalysis mechanism is depicted (Scheme 5) on the basis of the absolute configuration of the product and the control experiments (Table S3).[14] In the organocatalytic Michael reaction, the activated pyrazolone **2a** attacked the simultaneously activated isoxazole nitroolefin **1a** from the *Re*-face to deliver the adduct **A** via the transition state (**TS**). In the I_2-catalyzed oxidative homocoupling step, iodine and H_2O_2 produced the iodine radical; then, the stable C(sp^3)-H precursor **A** was transformed into an organic 3° radical **A-1** intermediate through hydrogen atom abstraction by a reactive iodine radical.[15] The chiral environment of intermediate **A-1** was retained. Finally, the intermediate **A-1** rapidly underwent radical-based homocoupling to furnish **4aa**. The excellent diastereoselectivity might be mainly attributed to the high ee and dr values of intermediate **A** and the high equilibrium ratio of the chiral diastereomer **A-1** during the dimerization. Subsequently, HI was oxidized to I_2 by H_2O_2 for the next cycle.

In conclusion, a novel method for the one-pot catalytic construction of C_2-symmetric axially chiral alkyl skeletons via asymmetric organo-/iodine sequential catalysis was developed. The current transformation allowed the synthesis of C_2-symmetric axially chiral pyrazolones and diones with a broad substrate scope with high yields (up to 99%), enantioselectivities (up to 99% ee), and excellent diastereoselectivities (up to >99:1 dr) under mild conditions without the use of metals and strong bases. The sequential catalytic protocol might be conducted via Michael addition, hydrogen atom abstraction, and then radical-based homocoupling.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02330.

General procedures, product characterization, copies of NMR spectra, HPLC chromatograms, and crystallographic data (PDF)

FAIR data, including the primary NMR FID files, for compounds **4aa**−**4cc**, **6aa**−**6cg**, **8aa**−**8ah**, and **A** (ZIP)

Accession Codes

CCDC 2015866 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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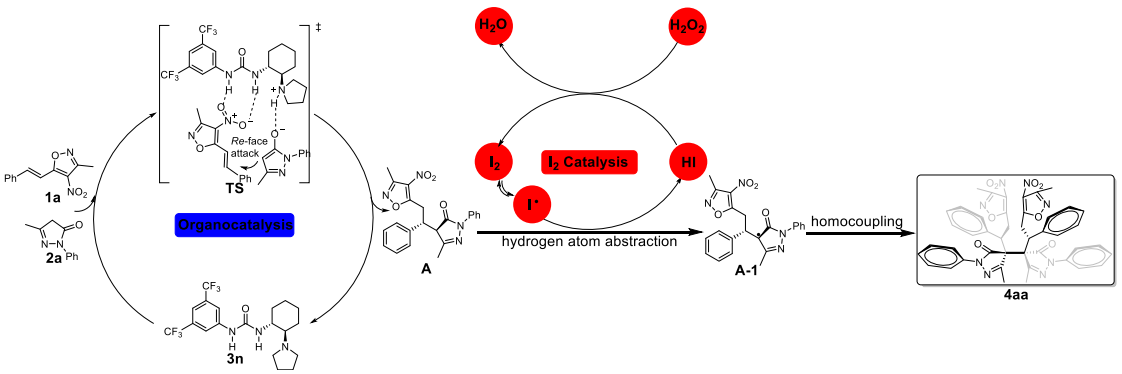
Scheme 5. Proposed Reaction Mechanism



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Notes

The authors declare no competing financial interest.

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