Cobalt-Catalyzed Regio-, Diastereo-, and Enantioselective Reductive Coupling of Internal Alkynes with Cyclobutenes

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Abstract:

While low-valent cobalt complex-catalyzed asymmetric reductive coupling of alkynes with acceptor-substituted alkenes is well-established, the reactions with unactivated alkenes have not been reported. Herein, we reported the cobalt-catalyzed asymmetric ene-yne reductive coupling of internal alkynes and unactivated cyclobutenes. The reaction produced densely functionalized chiral vinyl cyclobutanes up to 92% yields with excellent absolute and relative stereocontrol (>99% ee, >20:1 dr, and >20:1 *E*/*Z*), and high >20:1 regioselectivity. The scaled-up reaction and the post-synthetic derivatizations further elucidated the efficiency of the designed protocol. The preliminary mechanistic investigations suggested the involvement of zinc-mediated low-valent cobalt(I) complex generation, oxidative ene-yne cyclization, and protonation as the key mechanistic steps.

Introduction:

Optically active cyclobutanes are integral to many natural products and medicinally active molecules (Figure 1a).[1] They are also used as versatile structural motifs in organic synthesis.[2] Consequently, significant effort has been directed toward developing enantioselective methods for constructing densely functionalized cyclobutane frameworks. Among these, the protocols involving transition-metal catalyzed and photochemical [2+2] cycloaddition[3] and multi-step ring manipulation protocols[4] are notable (Figure 1b). However, these venerable methods are frequently limited by the specific decoration and functionalization of the starting materials. In comparison, easily made four-membered carbocycles provide a broader platform for diversification with functional groups.[5] Notable strategies include directing-group-controlled C–H functionalization of cyclobutanes,[6] enantioselective transformations of cyclobutanones,[7] and addition reactions involving cyclobutenes.[8] However, while C–H activation requires a directing group, enantioselective transformations of cyclobutanones remain primarily restricted to ketone enolate addition or reduction. In asymmetric functionalization of olefins, carbometallation is a critical step.[9] The process is driven by the release of olefinic strain in cyclic alkenes (Figure 1c).[10] For example, strain release is 27.7 kcal mol^{-1} for cyclopropenes and 4.8 kcal mol^{-1} for norbornene.[11] However, cyclobutene exhibits a much lower strain release (1.9 kcal mol^{-1}), limiting its reactivity involving carbometallation as a key step.[11] Despite this, several methods for enantioselective conjugate addition to activated cyclobutene have been documented, including copper-catalyzed borylation,[12] rhodium-catalyzed arylations with aryl boronic acids,[8b] and cobalt-catalyzed cyclopropanol-derived homoenolate addition (Figure

1d).[13] Achieving enantioselective C–C bond formation in nonpolar cyclobutene remains challenging.[11] Notable contributions include rhodium-catalyzed arylation and hydroacylation by Fletcher,[14] cobalt-catalyzed hydroalkynylation by Meng,[13] palladium-catalyzed enantioselective arylation by Lu,[6d] and the recent elegant cobalt-catalyzed reductive coupling of 1,1-disubstituted allenes by Meng.[15] However, intermolecular coupling of nonpolar cyclobutene with abundant π-components, such as internal alkynes, remains unexplored.

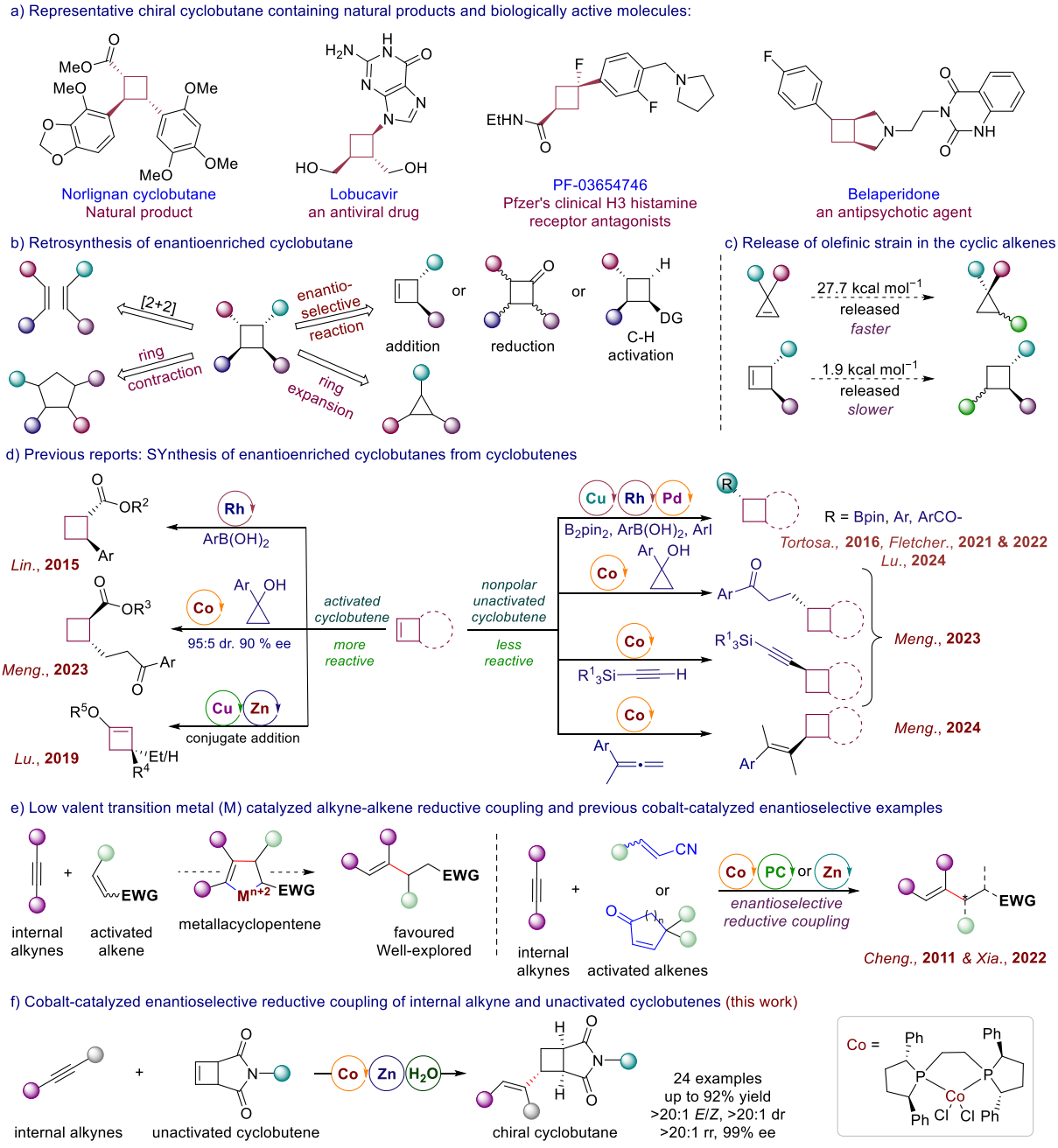


Figure 1. Application and synthesis of chiral cyclobutanes and their challenges. (a) Chiral cyclobutane containing natural products and bioactive compounds; (b) Methods for synthesizing cyclobutanes; (c) Strain in cyclic alkenes; (d) Previous reports synthesizing cyclobutanes from cyclobutenes; (e) Low valent TM catalyzed alkyne-alkene reductive coupling and previous cobalt-catalyzed enantioselective examples; (f) Cobalt-catalyzed

enantioselective reductive coupling of internal alkyne and unactivated cyclobutenes (this work).

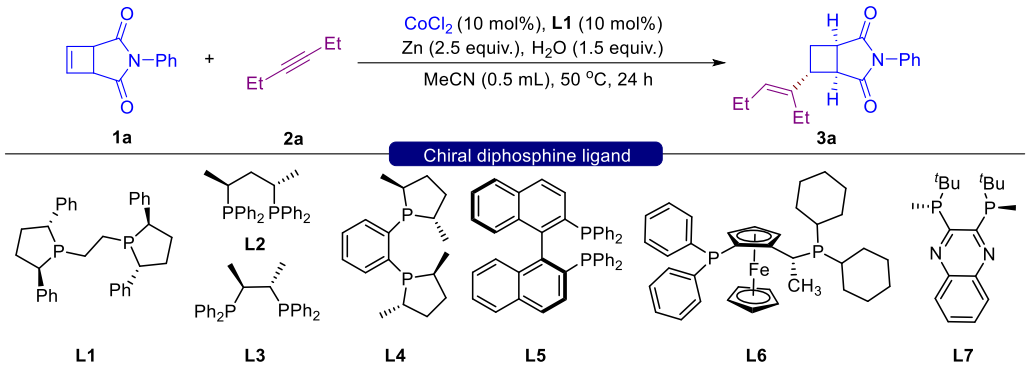
Intermolecular reductive cross-coupling of two π-components, promoted by low-valent transition metals, is a powerful strategy in organic synthesis.[16] This approach enables the construction of diverse C–C bonds using stable and readily available feedstocks, yielding densely functionalized sp^2 and sp^3 carbon frameworks without prefunctionalization.[17] Among these, alkyne–alkene reductive coupling is efficient, particularly with activated alkenes, proceeding via stable metallacyclopentene intermediates (Figure 1e).[18] Transition metals such as ruthenium, rhodium, cobalt, nickel, and palladium are widely used, with cobalt standing out due to its unique reactivity, abundance, low cost, and lower toxicity.[19] In the context of cobalt catalysis, Cheng reported the first example of asymmetric reductive coupling of alkynes with cyclic enones.[18d] More recently, Xia demonstrated asymmetric reductive coupling of alkynes with alkenyl nitriles via photoredox/cobalt dual catalysis.[18a] However, these methods are limited to activated alkenes. The stereo- and enantioselective reductive coupling of alkynes with unactivated alkenes, such as nonpolar cyclobutene, remains largely uncharted due to the inherently lower reactivity of unactivated alkenes (Figure 1f). The process is further complicated by challenges such as the formation of dienes through competitive β-hydride elimination and the generation of cyclobutenes via reductive elimination from the cobaltacyclopentene intermediate.[3d, 20] Additionally, mitigating potential alkyne oligomerization while simultaneously controlling regio- and enantioselectivity in the coupling with a low-reactivity alkene poses significant difficulties.[21]

We hypothesized that the unique reactivity of a cobalt complex featuring an optimal chiral diphosphine ligand could effectively control the regio-, stereo-, and chemoselectivity of the reductive cross-coupled product. Herein, we report cobalt-catalyzed chemo-, regio-, and enantioselective reductive coupling of internal alkynes with nonpolar cyclobutene through oxidative cyclization, enabling the synthesis of densely functionalized chiral vinyl cyclobutanes in moderate to good yields and excellent absolute and relative stereocontrol.

Results and Discussion

We began our investigation by choosing 3-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1a**) and 3-hexyne (**2a**) as the model substrates (Tables 1, S1-S11). The desired product **3a** was obtained in 32% GC yield with a very high 99% enantiomeric excess (ee) and >99:1 diastereomeric ratio (dr) in the presence of 10 mol% $CoCl_2$ as a cobalt precursor, 10 mol% **L1** as a chiral ligand, 2.5 equivalent zinc as the reductant, 1.5 equivalent H_2O as a proton source in acetonitrile at 50 °C for 24 h (Table 1, entry 1). The selection of cobalt salt and chiral ligand combination is crucial for the reaction, which mainly controls the reaction conversion, chemo- and stereoselectivity. When CoI_2, $CoBr_2$, and $Co(acac)_2$ were used instead of $CoCl_2$, the product **3a** was produced in poor yield, although the ee remains high (entry 2). In comparison, chiral diphosphine ligands significantly influenced the reaction's yield and ee (entries 3-8). Except for (*S*,*S*)-chiraphos (**L3**), all the tested ligands gave poor yield and poor ee of **3a**.

Table 1. Reaction development: Key optimizations[a]



Entry	Deviation from the above	Yield (%)	ee (%)	dr	*E*/*Z*
1	None	32	99	>20:1	>20:1
2	CoI_2, $CoBr_2$, $Co(acac)_2$, as Co-source	0 to 16	98	>20:1	>20:1
3	**L2** instead of **L1**	9	40	>20:1	>20:1
4	**L3** instead of **L1**	17	83.5	>20:1	>20:1
5	**L4** instead of **L1**	8	–15	>20:1	>20:1
6	**L5** instead of **L1**	54	–4	>20:1	>20:1
7	**L6** instead of **L1**	13	15	>20:1	>20:1
8	**L7** instead of **L1**	13	–24.5	>20:1	>20:1
9	60 °C instead of 50 °C	39	99	>20:1	>20:1
10	70 °C instead of 50 °C	27	99	>20:1	>20:1
11	THF instead of MeCN at 60 °C	62	99	>20:1	>20:1
12	DCM, MeOH or DMF instead of MeCN at 60 °C	<5 to 57	99	>20:1	>20:1
13	1.0. or 2.0 equiv. H_2O in THF at 60 °C	20, 54	99	>20:1	>20:1
14	2, or 3.0 equiv. of Zn	2 to 7	99	>20:1	>20:1
15	In or Mn (2.5 equiv.) instead of Zn	0 to 8	99	>20:1	>20:1
16	**20 mol% NaBArF in THF at 60 °C**	**79 (71)**	**99**	**>20:1**	**>20:1**
17	20 mol% $ZnCl_2$ or 50 mol% LiCl in THF at 60 °C	24 to 35	99	>20:1	>20:1
18	No Zn or no $CoCl_2$/**L1**	<5	--	--	--

[a]Reaction Conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), $CoCl_2$ (10 mol%), Ligand (10 mol%), Zn (0.25 mmol), H_2O (1.5 equiv.) in MeCN (0.5 mL) at 50 °C under Ar. Yields, diastereomeric ratio (dr), and *E*/*Z* ratio were determined by gas chromatographic analysis using 1,3,5-trimethoxy benzene as an internal standard. The isolated yield was given in the parenthesis. Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase column.

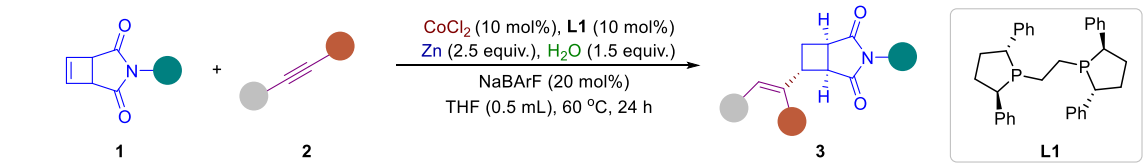
Slightly increasing temperature to 60 °C helps in the conversion of the reductive cross-coupled product without disturbing the ee and dr (entry 9). However, yield drops as the temperature is raised to 70 °C. The reaction was also sensitive to the solvent (entries 11-12). Notably, THF instead of acetonitrile gave the reductive coupled product with 62% yields with similar stereoselectivities (entry 11). However, other solvents gave inferior results (entry 12). The

amount of water is also crucial for this desymmetrization reaction (entry 13). 2.5 equivalent of Zn powder was found to be optimum for the reaction as increasing or decreasing the amount resulted in lower efficiency (entry 14). However, the product **3a** was produced in low yield when indium and manganese were utilized as the terminal reductant (entry 15). Furthermore, employing a catalytic quantity of sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (NaBArF) demonstrated the highest efficiency of the desired product of 79% GC yield (71% isolated yield) of **3a** with 99% ee, >20:1 dr and >20:1 *E*/*Z* ratio (entry 16). However, other additives are not so efficient in stabilizing the active cobalt complex, and lower yields were obtained (entry 17). Undoubtedly, the control experiments indicated that cobalt/L and zinc are essential for this asymmetric reductive coupling reaction (entry 18).

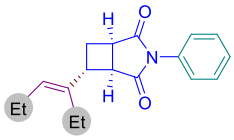
Taking the optimization conditions in hand, we checked the generality of the developed desymmetrization reaction (Table 2). Initially, **2a** was reacted with several nitrogen-substituted nonpolar cyclobutenes. The reaction tolerated diverse electron-donating (OMe), halogens (F, Cl, Br), and electron-withdrawing (CF_3) substituents containing functionalities at the different positions of the *N*-aryl ring, and the desired products **3b**-**3f** in 61-70% isolated yields with high >20:1 dr, >20:1 *E*/*Z* ratio and excellent 93% to >99% ee. (3,5-Dichloro)- and (2,4,6-trimethyl)-substitutions did not hinder the reaction, producing the desired products **3g** and **3h** in 60% and 62% isolated yield with good diastereo-, chemo- and enantioselectivity, respectively. Not only *N*-aryl substituents, aliphatic *N*-butyl and *N*-benzyl cyclobutenes were tolerated, giving the asymmetric reductive coupled products **3i** and **3j** in 92% and 40% yields with high >99% and 96% ee, respectively, while maintaining the same level of diastereo and chemoselectivity. Notably, the parent cyclobutene reacted under these conditions to produce the desired product **3k** in a moderate 38% yield with 82% ee, >20:1 dr, and >20:1 *E*/*Z* ratio.

The scope of the symmetric and asymmetric internal alkynes was then tested. The symmetrical 4-octyne reacted well and gave the product **3l** in moderate yield with 94% ee, >20:1 dr, and >20:1 *E*/*Z* ratio. Notably, the asymmetric prop-1-yn-1-ylbenzene also participated in this asymmetric reductive coupling and produced the target product **3m** in 74% yield with excellent 98% ee, >20:1 dr, >20:1 *E*/Z ratio and high 25:2 regioisomeric ratio (rr). Furthermore, (3-(benzyloxy)prop-1-yn-1-yl)benzene and hex-1-yn-1-ylbenzene were also suitable substrates, affording the products **3n** and **3o** in moderate yields and with high selectivities. Prop-1-yn-1-ylbenzenes with diverse electron-rich and electron-withdrawing functional groups at different positions of the aryl ring equally participated in this reaction, and the desired cross-coupled products (**3p**-**3v**) were isolated in 69–85% yields with excellent 86% to >99% ee with high chemo-, regio-, and diastereoselectivity. Several functional groups, including biaryl (**3q**), halogens (**3r**,**s**), nitrile (**3t**), ketone (**3u**), and amide (**3v**), are tolerated under these conditions. Notably, the yield and stereoselectivity were not affected by the heteroaromatic ring, as the quinoline and thiophene ring containing asymmetric alkyne successfully gave the desired products **3w** and **3x** in 86% and 65% yield, respectively, with >99% ee, >20:1 dr, >20:1 *E*/*Z* ratio and >20:1 rr. However, 3-phenyl-3-azabicyclo[3.2.0]hept-6-ene (**3y**) and 3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione (**3z**) were unable to give the desired products under standard condition which indicates that imide unit in nonpolar cyclobutene ring is very crucial for this asymmetric reductive coupling.

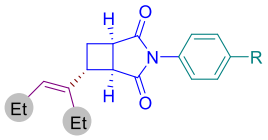
Table 2. Scope of the reaction.[a]



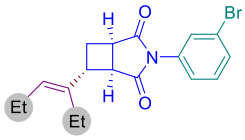
scope of cyclobutene



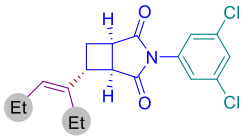
3a, 71%
>20:1 E/Z, >20:1 dr
99% ee



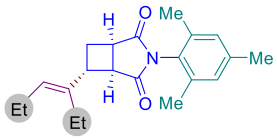
R= OMe; **3b**, 64%, >20:1 E/Z, >20:1 dr, 93% ee
= F; **3c**, 70%, >20:1 E/Z, >20:1 dr, 98% ee
= Cl; **3d**, 70%, >20:1 E/Z, >20:1 dr, 98% ee
= CF_3; **3e**, 74%, >20:1 E/Z, >20:1 dr, 94% ee



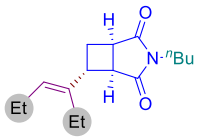
3f, 61%
>20:1 E/Z, >20:1 dr
>99% ee



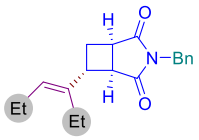
3g, 60%
>20:1 E/Z, >20:1 dr
98% ee



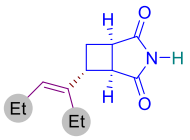
3h, 62%
>20:1 E/Z, >20:1 dr
94% ee



3i,92%
>20:1 E/Z, >20:1 dr
>99% ee

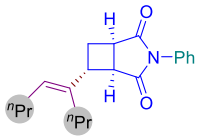


3j, 40%
>20:1 E/Z, >20:1 dr
96% ee

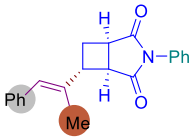


3k, 38%
>20:1 E/Z, >20:1 dr
82% ee

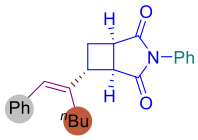
scope of the internal alkyne



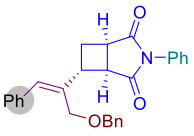
3l, 51%
>20:1 E/Z, >20:1 dr
94% ee



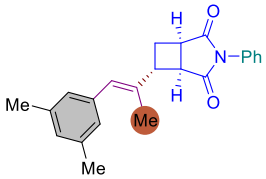
3m, 74%
>20:1 E/Z, >20:1 dr
25:2 rr, 98% ee



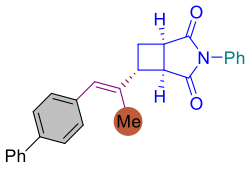
3n, 34%
>20:1 E/Z, >20:1 dr
>20:1 rr, 83% ee



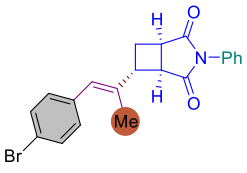
3o, 50%
>20:1 E/Z, >20:1 dr
>20:1 rr, 94% ee



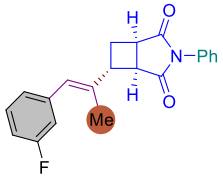
3p, 80%
>20:1 E/Z, >20:1 dr
7:1 rr, 96% ee



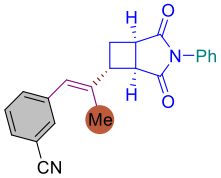
3q, 85%
>20:1 E/Z, >20:1 dr
25:3 rr, 97% ee



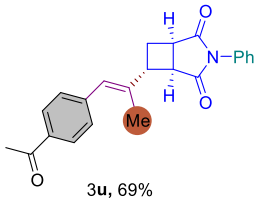
3r, 78%
>20:1 E/Z, >20:1 dr
>20:1 rr, 98% ee



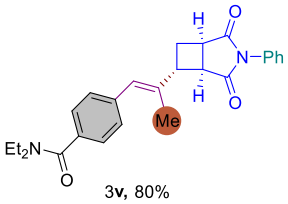
3s, 84%
>20:1 E/Z, >20:1 dr
25:2 rr, >99% ee



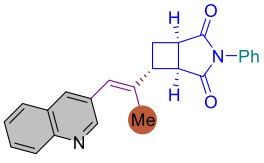
3**t**, 75%
>20:1 E/Z, >20:1 dr
>20:1 rr, >99% ee



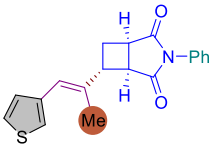
3**u**, 69%
>20:1 E/Z, >20:1 dr
>20:1 rr, 99% ee



3**v**, 80%
>20:1 E/Z, >20:1 dr
>20:1 rr, 99% ee



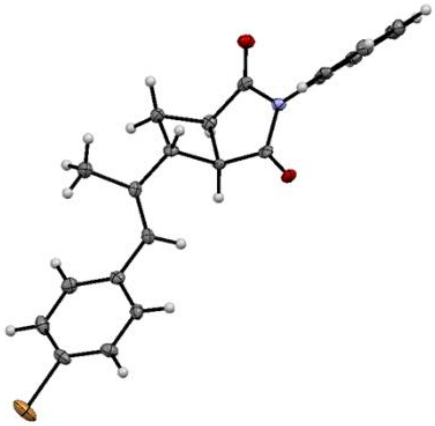
3**w**, 86%
>20:1 E/Z, >20:1 dr
>20:1 rr, >99% ee



3**x**, 65%
>20:1 E/Z, >20:1 dr
>20:1 rr, >99% ee

[a]Reaction Conditions: Table 1, entry 16. Diastereomeric ratio (dr), *E*/*Z* ratio, and regiomeric ratio (rr) were determined by ^{1}HNMR analysis of the crude mixture using 1,3,5-trimethoxy benzene as an internal standard. The isolated yield was given. Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase column.

The absolute stereochemistry of the product **3r** was determined to be 1*R*,5*S*,6*R* from the X-ray crystallography (Figure 2).[22] The configurations of the cyclobutanes in Table 2 were determined by analogy.



CCDC: 2429155.

Figure 2. Determination of absolute stereochemistry of "**3r**" from X-ray crystallography.

To show the synthetic potential of the cobalt-catalyzed asymmetric reductive coupling reaction, we performed the reaction on a mmol scale (Figure 3). The reaction produced the product **3a** with a 77% yield while maintaining excellent enantio-, diastereo- and chemoselectivity. We then performed a series of functional group transformations to showcase the synthetic applicability of the synthesized chiral cyclobutane product further. Product **3a** was first subjected to the alkene oxidative cleavage employing photoexcited nitroarenes.[23] The chiral cyclobutyl ketone **4** was isolated in 79% yield without significantly disturbing the stereochemistry of the product. Epoxidation reaction with mCPBA produced the epoxide **6** in 94% yield with moderate 1.2:1 dr. Additionally, the carbonyl group of the imide **3a** was reduced to tertiary amine in good yield without erosion of the stereochemistry of the product. Subsequently, the imide was fully reduced to the diol **7** in 35% yield via a three-step protocol.

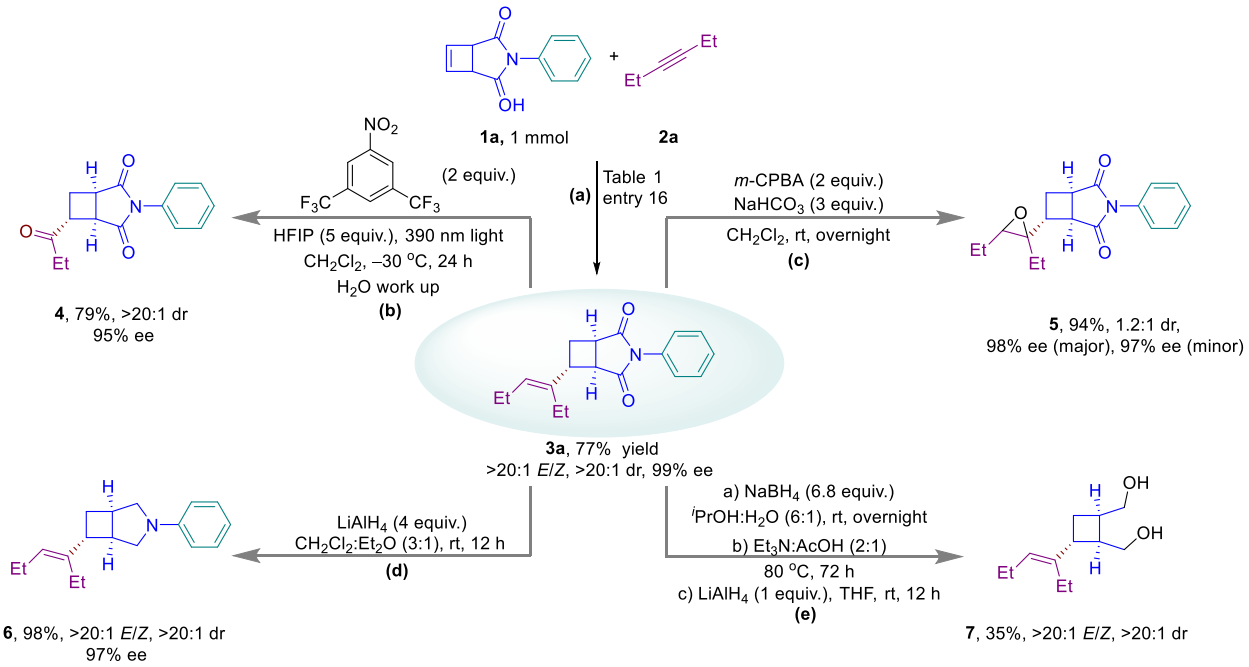


Figure 3. Synthetic Utility; (a) Scale up reaction of the "Standard conditions" = Table 1, entry 16, (b) Oxidative cleavage of the double bond of **3a**, (c) Epoxidation of **3a**, (d) Imide reduction of **3a**, (e) Complete reduction of imide in **3a.**

Control experiments were then performed to get further insight into the reaction mechanism (Figure 4). In the absence of H_2O, no reductive cross-coupled product was formed, which concludes that H_2O acts as the proton source of the reductive coupled product. This result was again confirmed when the reaction was performed in the presence of 1.5 equivalent of D_2O. The product **3a-d** was isolated in 74% yield, and ^1H NMR analysis indicated 62% and 100% D incorporation at "**a**" and "**b**" positions of the product, respectively.

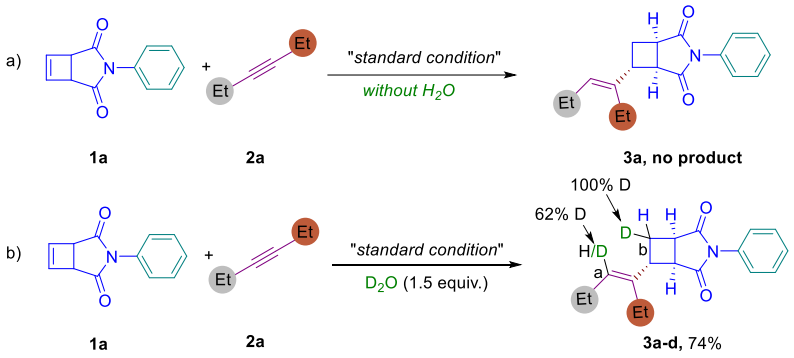


Figure 4. Mechanistic study; a) "Standard condition" without H_2O, b) "Standard condition" with D_2O.

Based on the control experiment and previous literature,[15, 18a, 24] a plausible mechanistic cycle was drawn (Figure 5). At first, zinc reduced the diphosphine-coordinated Co(II) precatalyst **I** to the low valent Co(I) complex **II**. NaBArF is known to stabilize the low-valent Co(I)-complexes by the anion metathesis.[25] Then, **1a** and **2a** coordinates with the Co(I) center to yield the intermediate **III**. This specific coordination of the p-bonds in this chiral environment causes oxidative cyclometalation, which results in the stereodefined cobaltacyclopentane intermediate **IV**. Then, double protolysis of **IV** by H_2O affords the product **3a** and Co(III) species **V**. Another single electron transfer by Zn reduced the Co(III) species to regenerate the Co(II) catalyst.

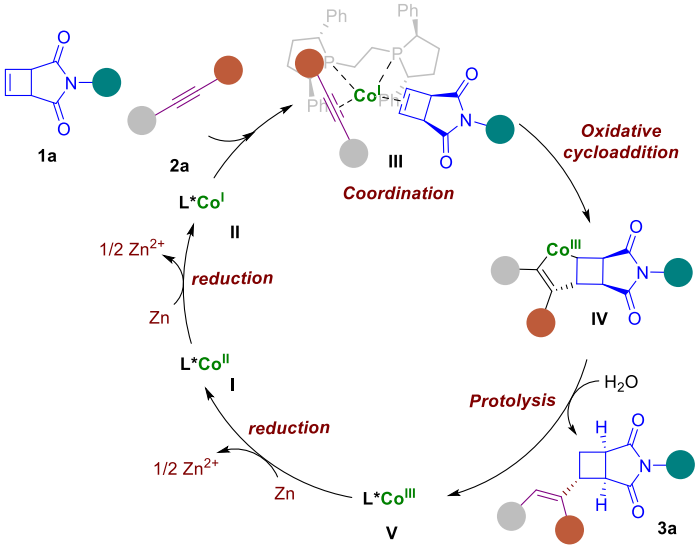


Figure 5. Proposed mechanism.

Conclusion

In conclusion, we achieved cobalt-catalyzed asymmetric ene-yne reductive cross-coupling of nonpolar cyclobutene and alkynes for the first time. The asymmetric vinyl cyclobutene products were isolated with up to 92% yields with excellent controls of absolute (>99% ee) and

relative (>20: 1 dr, >20:1 *E*/*Z*, and >20:1 rr) stereochemistry. Commercially available catalysts, ligands, and reducing agents were used. Control experiments and deuterium labeling have been performed to support the proposed catalytic cycle.

Author contributions

M.M. and B.M. conceived and designed the project. M.M. and S.R. performed the experiments. M.M. and B.M. wrote the manuscript. B.M. acquired the funding and directed the research.

Conflicts of interest

There are no conflicts to declare.

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Data availability

The data supporting this article have been included as part of the Electronic Supplementary Information.

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