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Letter

Cobalt-Catalyzed Chemoselective Transfer Hydrogenative Cyclization Cascade of Enone-Tethered Aldehydes

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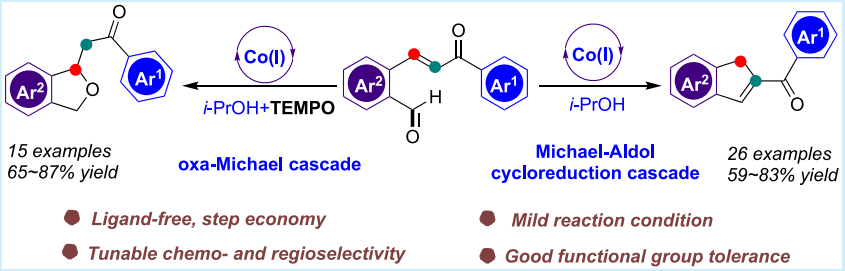
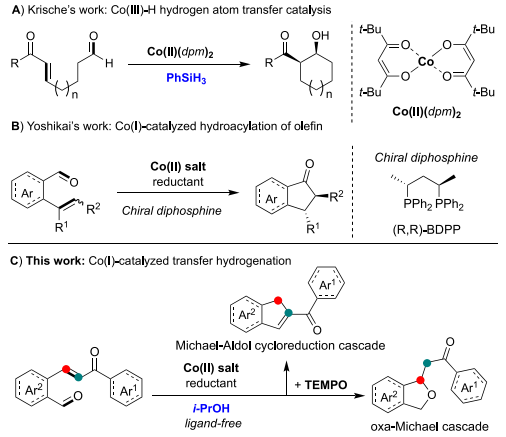


ABSTRACT: The ligand-free Co-catalyzed chemoselective reductive cyclization cascade of enone-tethered aldehydes with *i*-PrOH as the environmentally benign hydrogen surrogate is developed by this study. Mechanistic studies disclosed that such a protocol is initiated by an *ortho*-enone-assisted Co(I)-catalyzed reduction of the aldehyde functionality with *i*-PrOH. Meanwhile, the selectivity from the Michael−Aldol cycloreduction cascade to the oxa-Michael cascade is feasible and readily adjusted by the addition of steric Lewis bases, such as TEMPO and DABCO, delivering substituted 1*H*-indenes and dihydroisobenzofurans, respectively.

Cascade reactions represent an efficient chemical pathway to construct rather complex scaffolds and constitute a great challenge in modern organic chemistry and drug discovery.[1] To this end, chemoselective variation toward multifunctional substrates is generally a prerequisite to form precursors of the sequence. For instance, the intramolecular cyclization of enone-tethered electrophiles, such as aldehyde, ketone, enone, and nitro functionalities, provides a good setup for a Michael−Aldol coupling cascade reaction with nucleophiles to construct cyclic alcohol motifs.[2−4] However, such a Michael-addition-initiated cascade may be replaced by a nucleophilic attack on the more reactive electrophiles to alter the reaction sequence.[5,6] Despite a wealth of research on both cascades toward intramolecular enone-tethered aldehydes, transition-metal-catalyzed reductive cyclization remains less developed. Experimental investigations into the approach of chemoselective reductive cyclization and exploration of the different reactivities between two modes with the same catalyst would advance the potential of such strategies in depth.

The Co-catalyzed diastereoselective Michael−Aldol cycloreduction with a stoichiometric amount of silanes was pioneered by the Krische group (Scheme 1A), which continued the catalytic cycling between Co(I) and Co(III).[7] Recently, Co-catalyzed reductive π-unsaturated bonds with inexpensive and sustainable hydrogen (H) surrogates have been accessed.[8] C/N alkylation with alkanols, proceeding through a hydrogen-borrowing strategy, was thereafter developed.[9] Our group was contemporaneously focusing on Co-catalyzed transfer hydrogenations. As a result, the Co(I)/diphosphine-catalyzed chemoselective hydrogenation of C═C and C═O bonds with alkanols was developed.[10]

Scheme 1. Cobalt-Catalyzed Intramolecular Coupling of Aldehydes with π-Unsaturated Bonds



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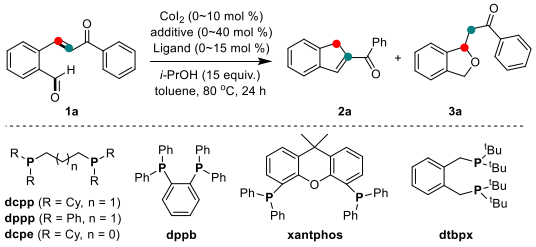
We thus envisioned that such a system may enable the conjugate reduction of enones to afford enolate nucleophile for the intramolecular attack to aldehydes. But the competitive *ortho*-vinyl-assisted Co(I)-catalyzed reduction of aldehydes, followed by oxa-Michael cyclization, cannot be completely excluded. In fact, the successive cross-coupling of alkanols with olefins to offer ethers under Co(II) catalysis was feasible following either aerobic oxidative cyclization[11] or a hydrogen-atom transfer and radical-polar crossover strategy.[12] An additional challenge is to suppress the potential intramolecular hydroacylation of olefins documented by Yoshikai's group (Scheme 1B).[13] In this study, we report the first example of the low-valent Co-catalyzed reductive cyclization of enone-tethered aldehydes with isopropanol (*i*-PrOH) (Scheme 1C). To our surprise, the Michael−Aldol cycloreduction cascade proceeds smoothly without ligands and is terminated with a dehydration step to provide 1*H*-indene derivatives. By contrast, the selectivity to the oxa-Michael cascade can be readily adjusted with the addition of Lewis bases, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 1,4-diazabicyclo[2.2.2]octane (DABCO), delivering the substituted dihydroisobenzofurans.

The Co-catalyzed transfer hydrogenative cyclization of **1a** was conducted with an in-situ-generated Co(I)-diphosphine catalyst and *i*-PrOH (Table 1 and Table S1). As a result of

Table 1. Condition Optimization for the Michael−Aldol Cycloreduction of 1a[a]



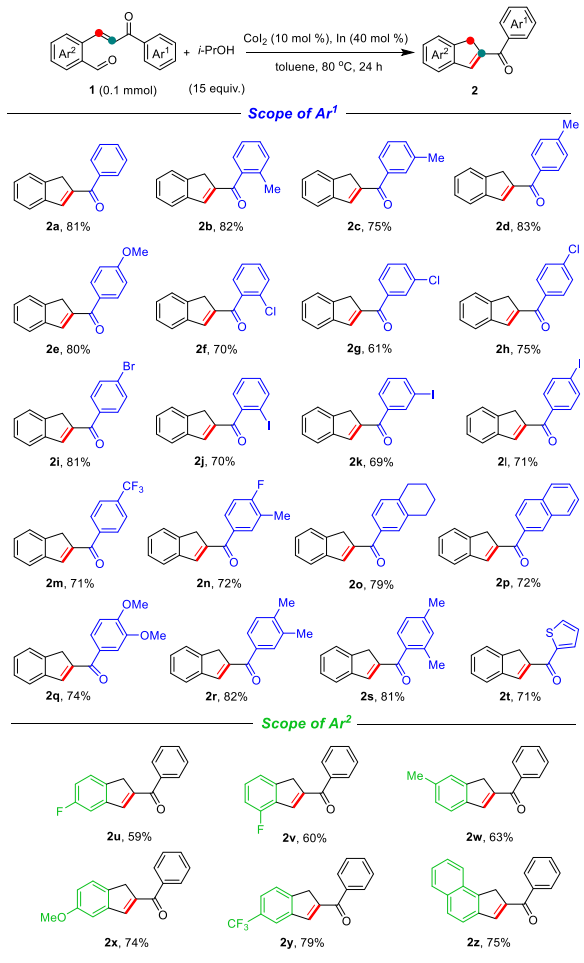
entry	[Co]	ligand	additive (mol %)	conv. (%)[b]	2a/3a
1	CoI_2	dcpp	In (40)	72	2:1
2	CoI_2	dppp	In (40)	64	2:1
3	CoI_2	dppb	In (40)	70	6:1
4	CoI_2	dcpe	In (40)	37	1:1
5	CoI_2	xantphos	In (40)	31	3:4
6	CoI_2	dtbpx	In (40)	91	4:1
7	**CoI_2**		**In (40)**	**93**	**8:1**
8	CoI_2			0	
9			InI_3 (10)	0	

[a]General conditions: **1a** (0.1 mmol), CoI_2 (10 mol %), ligand (15 mol %), toluene (0.5 mL), under Ar. [b]Conversion was determined by ^{1}H NMR using 2-methylindole as the internal standard.

preliminary examinations, the reaction was carried out with CoI_2 (10 mol %), dcpp (15 mol %), indium powder (In) (40 mol %), and *i*-PrOH (10 equiv) in toluene at 80 °C for 24 h under argon (Table 1, entry 1). Instead of the cyclic alcohol upon a typical Michael−Aldol coupling cascade,[3,4] appreciable quantities of the indene counterpart **2a**, featuring an indenyl ^{1}H NMR signal at δ 7.49 and δ 3.88, were formed. Notably, de Bruin reported the transformation of *o*-cinnamyl *N*-tosyl hydrazones to substituted 1*H*-indenes, facilitated by the native reactivity of a Co(III) carbene radical intermediate.[14] The oxa-Michael product **3a** was also obtained, but in less yield. From the typical ^{1}H NMR resonance of secondary CH at δ 3.88 for **2a** and tertiary CH at δ 5.93 for **3a**, a ratio of ca. 2:1 was determined. The structural recognition of both products upon isolation was confirmed by 2D ^{13}C/^{1}H HETCOR (HMQC and HMBC) experiments. We next screened selected bidentate phosphine ligands, which differed in their respective bite angles and functionalities (entries 2−6), thereby tuning the coordination mode of either enone or aldehyde with the Co center to improve the chemoselectivity and reactivity. Evidently, different yields of **2a** and **3a** were detected. However, it is difficult to elucidate the precise pathway by which the type of ligand influences the reaction. As shown, the steric dtbpx significantly improved the reactivity, giving a total yield of 91% with a moderate ratio of **2a** to **3a**. Surprisingly, this result is comparable to that without ligands (entry 7). Further studies demonstrated that the in situ generation of low-valent Co(I) species was indispensable (entry 8). In addition, the Lewis acidic InI_3 (10 mol %) formed in situ could not provide the desired reductive coupling (entry 9).

Subsequently, the limit and scope of this protocol were studied (Scheme 2). We observed that electronic variation of the phenyl group (Ar^1) adjacent to the carbonyl site of the enone affects the reactivity. Specifically, the cyclized products substituted with electron-withdrawing groups at the para position (**2h**, **2i**, **2l**, and **2m**) were obtained in slightly higher

Scheme 2. Co-Catalyzed Michael−Aldol Cycloreduction Cascade Leading to 1*H*-Indenes (2)[a]



[a]Reaction conditions: toluene (0.5 mL), under Ar, isolated yield.

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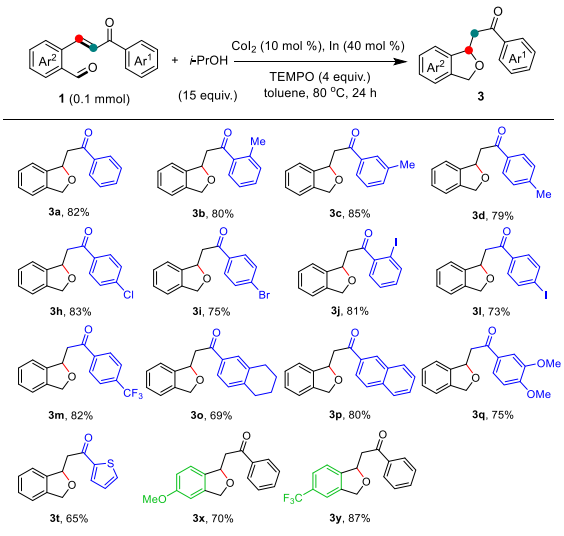
yields compared with those with electron-donating groups (**2d** and **2e**). In addition, the performance decreased in the order of para (**2d**/**2h**/**2l**) > ortho (**2b**/**2f**/**2j**) > meta (**2c**/**2g**/**2k**) regardless of the electronic property, suggesting that both the nucleophilicity and the stabilization of the transient α-carbon nucleophile play a crucial role in the cyclization. On the contrary, the steric hindrance of the Ar^1 has nearly no influence. Various disubstituted phenyl ring such as *p*-F/*m*-Me (**2n**), *p*-OMe/*m*-OMe (**2q**), *p*-Me/*m*-Me (**2r**), and *p*-Me/*o*-Me (**2s**) were tolerated and provided the corresponding 1*H*-indenes in 72−82% yields. The reductive cyclization also proceeded smoothly when the Ar^1 was replaced by either naphthyl derivatives (**2o** and **2p**) or heteroaromatic thiophene (**2t**). Finally, the functionalities of the phenyl group (Ar^2) at the bridge with such a protocol were examined. Substituents with not only electron-withdrawing (**2u**, **2v**, **2y**, and **2z**) functionalities but also electron-donating groups (**2w** and **2x**) were found to be tolerated. We also investigated the Michael−Aldol cycloreduction of **1a** on a scale of 4.24 mmol, which provided **2a** in an acceptable yield of 71% under the optimum conditions (Scheme S3).

On the basis of our previous studies[10] and the present results, this low-valent Co-catalyzed Michael−Aldol cycloreduction may proceed via the famous Meerwein−Ponndorf−Verley reduction route.[15] To identify whether it follows a concerted or stepwise fashion, the poisoning studies using TEMPO as an inhibitor were performed (Table S3). To our surprise, the formation of **2a** was significantly suppressed with the addition of TEMPO, whereas the yield of **3a** increased. We rationally suspected that the hydrogen transfer leading to the Michael−Aldol cycloreduction product (**2**) proceeds via the transiency Co−H species. In contrast, the oxa-Michael route to **3** occurs mainly in a concerted fashion. These two paths are in competition. Having clarified the selectivity to each cascade under the present protocol, we turned our attention to the optimum conditions leading to **3** and its substrate tolerance (Scheme 3). As a result, the best yield of **3a** (82%) was obtained with the addition of 4 equiv of TEMPO. In addition, enone-tethered aldehydes with functionalities at both sites of Ar^1 and Ar^2 were tolerated, wherein neither an electronic nor a steric effect has been remarkably detected.

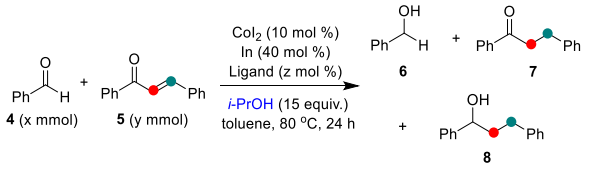
Scheme 3. Co-Catalyzed oxa-Michael cascade Leading to Dihydroisobenzofurans (3)[a]



[a]Reaction conditions: toluene (0.5 mL), under Ar, isolated yield.

The potential for performing an intermolecular Michael−Aldol reductive coupling was also evaluated under standard conditions, taking the reaction of benzaldehyde (**4**) with chalcone (**5**) as an example (Table 2, entry 1). Unfortunately,

Table 2. Cross Experiments on the Intermolecular Michael−Aldol Reductive Coupling[a]



				yield (%)[b]		
entry	**4** (*x*)	**5** (*y*)	ligand (*z*)	**6**	**7**	**8**
1	(0.1)	(0.1)	(0)	44	0	0
2	(0.1)	(0.02)	(0)	38	0	0
3	(0.1)	(0)	(0)	6		
4	(0.1)	(0.1)	dtbpx (15)	58	0	0
5	(0.1)	(0.02)	dtbpx (15)	8	0	0
6	(0)	(0.1)	(0)		0	0
7	(0)	(0.1)	dtbpx (15)		1	0
8	(0)	(0.1)	dcpp (15)		14	84
9	(0)	(0.1)	dcpe (15)		0	98

[a]Reaction conditions: toluene (0.5 mL), under Ar. [b]Yields were determined by ^{1}H NMR using CH_2Br_2 as the internal standard.

the desired two-component cascade addition product was not detected. Instead, only the reduction of **4** partially proceeded, and a catalytic amount of **5** was sufficient but necessary for such a transformation (entries 2 and 3). The addition of dtbpx (15 mol %) did not improve the reactivity (entry 4 vs entry 1). Meanwhile, a stoichiometric amount of **5** was required to obtain a comparative efficiency (entry 4 vs entry 5). This is due to the preferred coordination to Co(I) with dtbpx over **5**, whereas the latter functions as the active site for the reduction of **4**. To ascertain whether the reductive cyclization leading to **2** proceeds via the typical Michael−Aldol coupling cascade and whether the varied reactivities under study differ from the reactivity of the Michael reduction of enones, chalcone (**5**) was subjected to the optimum conditions (entry 6). To our surprise, **5** remained unchanged. In addition, the reduction of **5** proceeded poorly in the presence of dtbpx (entry 7), dppb, xantphos, and dppp (Table S2) but readily occurred with dcpp and dcpe (entries 8 and 9). Collectively, a high efficiency in the Michael reduction of enones did not promise the formation of 1*H*-indene **2** over dihydroisobenzofuran **3**. The aldehydes were preferentially reduced in the presence of an enone functionality, most likely functioning as the ligand.

Deuterium labeling experiments with the purpose of obtaining insights into the route leading to such a Michael−Aldol cycloreduction cascade were conducted (Table 3). Consequently, the benchmark reaction was carried out with $(CD_3)_2CDOH$ (*i*-PrOH-d_7) and $(CD_3)_2CDOD$ (*i*-PrOH-d_8), respectively. The five-membered ring of **2a**−**d** is significantly deuterated, delivering a full deuteration at the methylene (H^a−H^b) with a high percentage (>60%). In addition, the deuterium content is almost the same with two H surrogates. This suggests that the tertiary CH in *i*-PrOH, rather than the hydroxyl group, functions as a H source in the formation of **2a**.

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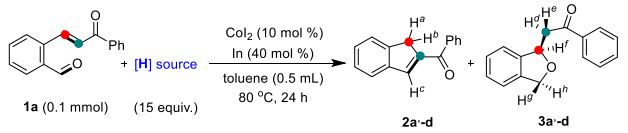
Table 3. Deuterium Labeling Experiments[a]



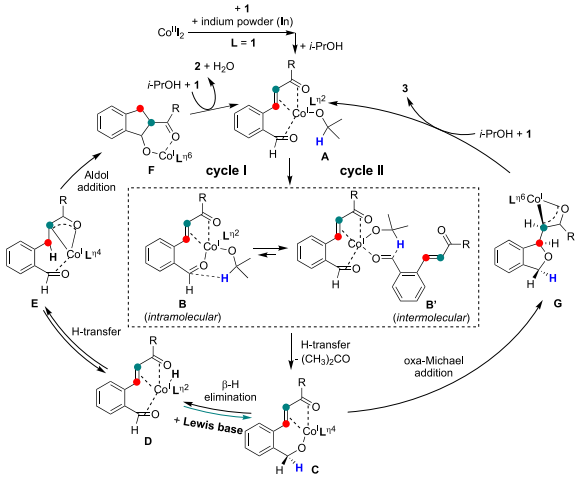
	yield (%)[b]		D occupation (D %)						H–H/H–D/D–D		
[H]	2a-d	3a-d	H^a/H^b	H^c	H^d	H^e	H^g	H^h	H^a-H^b	H^d-H^e	H^g-H^h
i-PrOH-d_8	60	15	80	50	65	40	40	40	10:21:69	25:45:30	20:80:0
i-PrOH-d_7	64	13	74	20	50	15	40	40	10:30:60	35:65:0	20:80:0

[a]Reaction conditions: toluene (0.5 mL), under Ar. [b]Isolated yield.

Moreover, there is nearly no proton–hydride exchange during such a process. Herein the formation of **3a** is non-enantioselective, but only one enantiomer is displayed for clarity. We observed that the deuterium content of the methylene group at the ring (H^g–H^h) does not vary with H surrogates, whereas those adjacent to the carbonyl site (H^d–H^e) differ remarkably. These results indicate that the oxa-Michael addition in the formation of **3a** is a fast and nonreversible step.

In the light of the literature and our present results, a tentative reaction mechanism is proposed and outlined in Scheme 4. It contains two catalytic cycles of **I** and **II**,

Scheme 4. Proposed Mechanism



representing the pathways to **2** and **3**, respectively. Both cycles initiate after the formation of **A** from the reduction of CoI_2 and the subsequent nucleophilic substitution of iodide with *i*-PrOH. It is noteworthy that the low-valent Co(I) can be coordinated by **1** in either the (η^2, η^6) or the (η^4, η^4) mode to satisfy the electronic and geometric requirements. Herein only one of them is demonstrated to clarify the main pathway. As confirmed by experiments, the subsequent hydrogen transfer in a concerted fashion to the aldehyde is preferred over the enone functionality. Complex **C** is thus formed with the dissociation of an acetone. In detail, we supposed that the intramolecular transfer via **B** is unlikely because the cyclic six-membered ring therein is highly distorted. Instead, the formation of a flat six-membered ring at the stable 18-electron Co(I) by coordination with another **1** in **B′** renders the hydrogen transfer plausible. Next, β–H elimination in **C** occurs to give **D** for cycle **I**, followed by hydride transfer from Co to the enone site, resulting in the cobalt-enolate **E**. The subsequent aldol addition provides **F**, which is thereafter terminated with a dehydration step to deliver **2** and regenerate **A** by further reaction with **1** and *i*-PrOH. The presence of Co-enolate **E** was confirmed by subjecting the saturated ketone-tethered aldehyde **9a** to the optimum conditions (Scheme S2), which provides **2a** in only 33% yield. For cycle **II**, complex **C** undergoes oxa-Michael addition directly, providing the Co-enolate **G**. Next, the nucleophilic substitution of enolate with *i*-PrOH and the coordination with another **1** regenerates **A**, coincidingly offering **3**.

Under the optimized conditions, the β–H elimination in **C** takes place prior to the competitive oxa-Michael addition, thus affording 1*H*-indene (**2**) as the major product. However, the reversed hydride transfer from Co(I) to carbonyls is accelerated with Lewis bases of proper steric and electronic properties,[16] such as TEMPO. Thus the conversion from **C** to **D** becomes reversible, and the oxa-Michael addition leading to **3** is thereby dominant. To confirm this opinion, a variety of Lewis basic amines were examined as the substitute for TEMPO, wherein the steric DABCO performs comparably (Table S4). In this regard, it is partially understandable that the selectivity varied with different steric bidentate phosphines.

In summary, the ligand-free low-valent Co-catalyzed chemoselective transfer hydrogenative cyclization cascade of enone-tethered aldehydes with *i*-PrOH as the environmentally benign H surrogate was developed. The selectivity from 1*H*-indenes to dihydroisobenzofurans could be readily adjusted by the addition of Lewis bases. New perspectives could be obtained by this study to solve some prominent problems in the field of cobalt catalysis. For example, the challenging Co-catalyzed β–H elimination[9d,10] and the impeded hydride transfer from Co(III)–H species to carbonyl moieties[10,13,16] can be approached by launching a proper cobalt valence and chelate environment. Further studies toward the Co-catalyzed enone-trigged cascade reactions are currently under way.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00992.

Detailed experimental procedures and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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