Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202001353

Link to VoR: https://doi.org/10.1002/adsc.202001353

10.1002/adsc.202001353

COMMUNICATION

DOI: 10.1002/adsc.202((will be filled in by the editorial staff))

Kinetic Resolution and Dynamic Kinetic Resolution of γ-Aryl-substituted Butenolides via Copper-Catalyzed 1,4-Hydroboration

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Kinetic resolution (KR) and dynamic kinetic resolution (DKR) of γ-aryl and heteroaryl-substituted butenolides via CuH-catalyzed 1,4-hydroboration using pinacolborane is reported. With a copper-Ph-BPE catalyst, selectivity factors were extremely high (*s* = >400) with regard to the kinetic resolution of β-methyl-γ-phenyl butenolide; DKR was possible in the presence of an amine base (DBU), which facilitated racemization of the starting unsaturated lactones. The reaction provided easy access to highly enantioenriched γ-butyrolactones (>99% ee) containing β,γ-substituents.

Keywords: Copper; Dynamic kinetic resolution; Hydroboration; Kinetic resolution; Lactones

Copper-hydride (CuH) catalyzed asymmetric reduction with silanes has been established as a powerful synthetic method in organic synthesis.[1] Due to the low cost of copper salts, easy accessibility of reducing silane reagents and chiral ligands, high selectivity, and mild reaction conditions for copper-hydride catalysis, the process has become a practical method for synthetic chemists.

Dynamic kinetic resolution (DKR) is an effective approach for preparation of enantiomerically enriched compounds compared to traditional kinetic resolution, given the expected yield and efficiency of the process.[2] While a number of transition metal-catalyzed asymmetric hydrogenation and transfer hydrogenation reactions of organic compounds through dynamic kinetic resolution including rare Ir, Rh, Pd, and Ru catalysts have been reported,[3] few DKR examples have been reported via CuH catalysis[4,5] in asymmetric reductions involving silanes and hydrogen[4c] as a stoichiometric reducing agent. Our group previously reported that stable pinacolborane (pinBH) could be used for generation of copper-hydride instead of hydrosilanes, which was applied to hydroboration of alkenes and alkynes,[6] and 1,4-hydroboration of coumarins.[7] Since generation of copper-hydride species from suitable copper precursors and pinacolborane has become possible under mild conditions without alkoxide bases,[6d,e,g,7] we decided to expand our hydroboration method to kinetic resolution of unsaturated compounds.

In 2005, Buchwald and coworkers first utilized β,γ-disubstituted butenolides as the subject of DKR through copper-catalyzed asymmetric conjugate reduction in an effort to achieve asymmetric total synthesis of eupomatilone-3.[4b] However, all other butenolide substrates containing a simple aryl group at the γ-position differed from the unsaturated lactone precursor for eupomatilone synthesis,[8] resulting in moderate enantioselectivity (67–87% ee) and remained a challenge. Therefore, we initiated an investigation with γ-phenyl butenolide, *rac*-**1a**, as a model substrate, with the goal of finding a highly enantioselective ligand-copper catalytic system for 1,4-hydroboration of β,γ-disubstituted butenolides (Table 1). Use of copper(I) chloride and NaO*t*Bu as catalytic precursors in the presence of C_2-symmetric tol-BINAP ligand (**L1**) and pinacolborane was not effective, resulting in racemic **2a** with poor mass balance (entry 1). Therefore, we changed the precursor to a copper carboxylate such as CuOAc and CuTC, which could be activated by pinacolborane in the absence of an alkoxide base. However, **L1** displayed low reactivity and selectivity under both conditions (entries 2 and 3). Changing the ligand to the bulkier dtbm-Segphos (**L2**), a highly efficient ligand for hydroboration of alkenes,[6b,c] yielded improved selectivity (*s* = 17) with reduced reaction time (entry 4). Further ligand screening showed that MeO-BIPHEP (**L3**) was more selective than **L2** or the P-chiral QuinoxP* ligand (**L4**) (entries 5 and 6). Finally, Josiphos (**L5**) and Ph-BPE (**L6**) ligands were highly selective and reactive in the kinetic resolution reaction; the BPE ligand (**L6**) finally was chosen as the optimal ligand for kinetic resolution of *rac*-**1a** (entry 8). Moreover, in the absence of a phosphine ligand, the reaction did not proceed (entry 9), indicating that hydroboration of **1a** with CuTC and **L6** was a true

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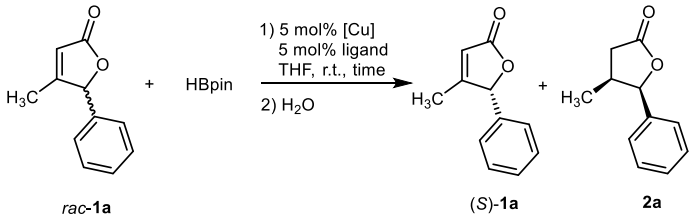
ligand-accelerated reaction with no background reduction. In contrast, addition of NaO*t*Bu yielded a

Table 1. Optimization of the kinetic resolution of *rac*-**1a**.[a]



Entry	[Cu]	Ligand	Time [h]	Conv. [%][b]	Yield [%][c]	ee of (*S*)-**1a** [%][d]	ee of **2a** [%][d]	*s*[e]
1	CuCl/ NaO*t*Bu	**L1**	24	68	35	–	0	–
2	CuOAc	**L1**	72	38	38	8	13	1.4
3	CuTC[f]	**L1**	72	35	28	8	15	1.5
4	CuTC	**L2**	2	48	46	71	71	17
5	CuTC	**L3**	12	46	47	74	87	32
6	CuTC	**L4**	3.5	49	46	63	66	9.2
7	CuTC	**L5**	0.2	51	45	95	92	93
8	CuTC	**L6**	1.2	50	50	98	98	458
9	CuTC	None	24	0	–	–	–	–
10	CuTC/ NaO*t*Bu	None	24	50	39	–	–	–

[a] General reaction conditions: *rac*-**1a** (0.3 mmol), HBpin (0.6 mmol), [Cu] (0.015 mmol) and ligand (0.015 mmol) in THF (1 mL).
[b] Conversion of **1a** was determined by GC analysis using tetradecane as an internal standard.
[c] Isolated yield of **2a**.
[d] The % ee was determined by HPLC analysis on a chiral phase.
[e] Selectivity factor, $s = \ln[(1–c)(1–ee)]/\ln[(1–c)(1+ee)]$.
[f] Copper(I) thiophene-2-carboxylate.

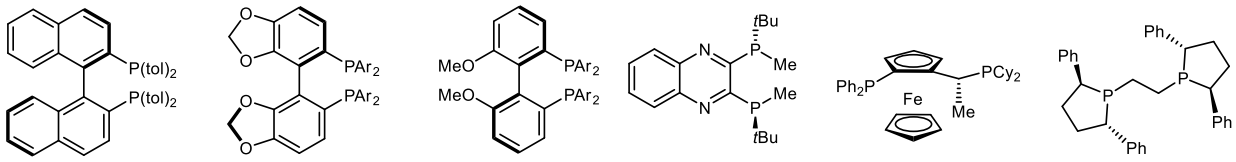


Figure 1. Structure of ligands.

significant quantity of the *rac*-**2a** product even in the absence of ligand (entry 10), suggesting that a significant background reaction is possible during the reaction.

We then briefly carried out KR of butenolides containing bulkier β-substituent, such as isopropyl and phenyl using the optimized conditions found in the KR of *rac*-**1a** (Scheme 1). Both substrates reached around 50% conversion in an extended reaction time, but with good selectivity factors.

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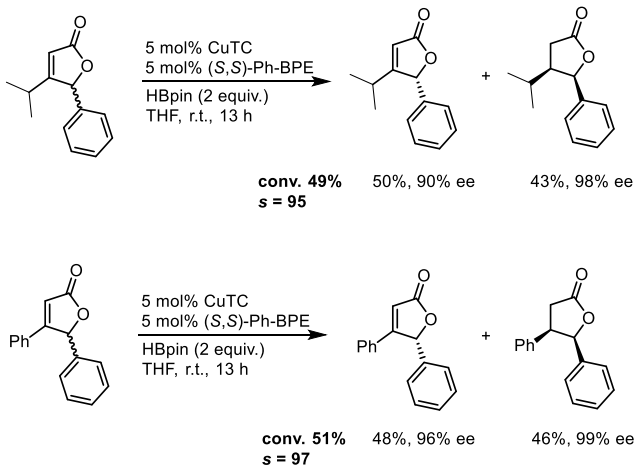
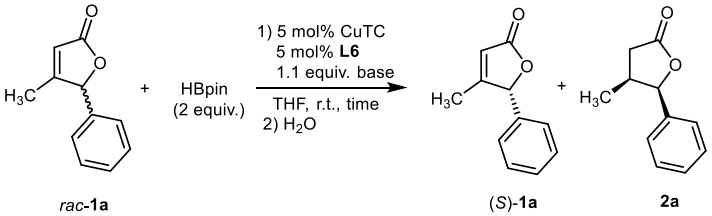


Scheme 1. Kinetic resolution of butenolides.

Table 2. Optimization of the dynamic kinetic resolution of *rac*-**1a**.[a]



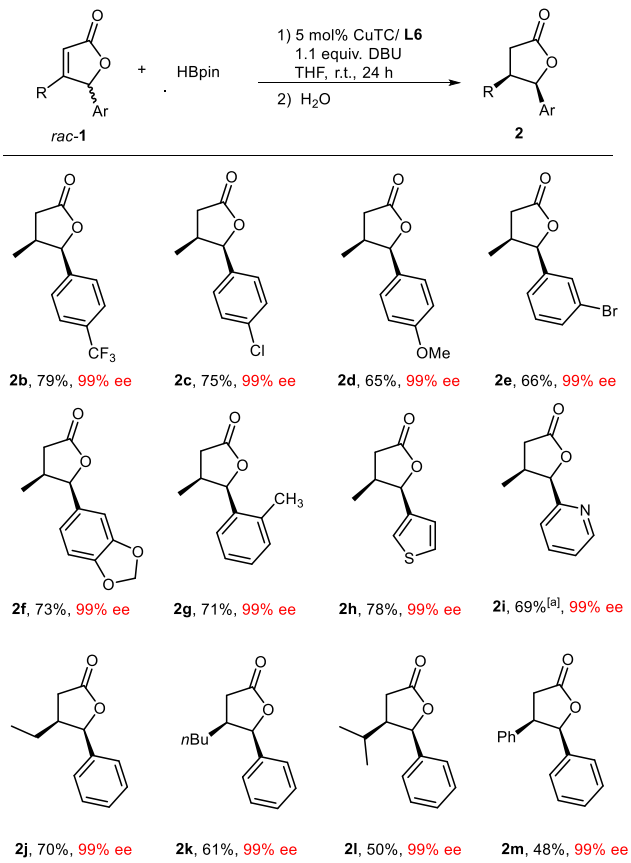
Entry	Base[b]	Time [h]	Conv. [%][c]	Yield [%][d]	ee of **1a** [%][e]	ee of **2a** [%][e]
1	NaO-*t*Bu	24	28	20	0	56
2	Cs_2CO_3	12	82	78	10	60
3	TEA	12	80	72	23	97
4	DIPEA	12	57	56	95	93
5	DIPA	12	55	53	84	95
6	DABCO	12	85	79	17	93
7	DBN	12	66	57	13	95
8	DBU	12	76	66	15	99
9	DBU	24	84	78	19	99
10[f]	DBU	36	90	85	47	99

[a] General reaction conditions: **1a** (0.3 mmol), HBpin (0.6 mmol), CuTC (0.015 mmol), (*S*,*S*)-Ph-BPE (0.015 mmol) and base (0.33 mmol) in THF (1 mL).
[b] TEA = trimethylamine, DIPEA = *N*,*N*-diisopropylethylamine, DIPA = diisopropylamine, DABCO = 1,4-diazabicyclo [2.2.2]octane, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
[c] Conversion was determined by GC analysis and ^{1}H NMR analysis using tetradecane and DMF, as an internal standard, respectively.
[d] Isolated yield of **2a**.
[e] The % ee was determined by HPLC analysis of chiral phase.
[f] The reaction was conducted at 0 ˚C.

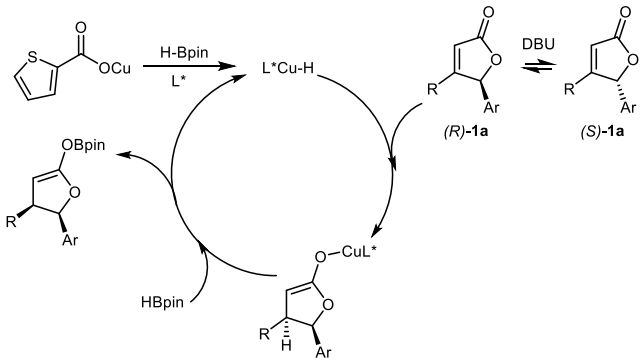
Next, we sought to extend the kinetic resolution method to the DKR of the unsaturated lactone **1a** using a highly stereoselective copper-**L6** catalyst (Table 2). In most reported DKR examples using CuH catalysis, use of an alkoxide base was necessary for catalyst activation and racemization of the starting substrates such as enones, lactones, and unsaturated esters.[4,5] However, in our hydroboration case, NaO*t*Bu was not compatible with the catalytic conditions, resulting in low conversion and a low ee value of the product due to background reduction (entry 1). Therefore, we attempted to use other bases to facilitate racemization of *rac*-**1a**, and found that amine bases were generally compatible and produced an increased yield and high ee of **2a** (entries 3–8). Triethylamine resulted in 97% ee of reduction product **2a** with significantly racemized starting material **1a**. However, bulky isopropyl-substituted amines such as DIPEA and DIPA were not suitable for facile racemization of the starting material (entries 4 and 5). Cyclic amines were more efficient than TEA in terms of racemization of the starting material (entries 6–8), and DBU was selected as optimal for the DKR process (entry 8). Elongation of reaction duration resulted in additional conversion and increased yield of chiral **2a** in 99% ee

(entry 9); however, reducing the reaction temperature to 0 ˚C led to slower racemization (entry 10).

On the basis of the success of the DKR of *rac*-**1a**, we next examined the scope of the DKR method for other γ-aryl-substituted unsaturated lactones (Scheme 2). All reduction products (**2b**–**2i**) were formed from γ-aryl-β-methyl butenolides with high enantioselectivity (>99%) without formation of other stereoisomeric products. Substrates with an electron withdrawing substituent (-CF_3, -Cl, -Br) on the aromatic group or electron donating substituent were all reactive, suggesting no clear dependence on an electronic factor. Ortho-substituted aryl (**1g**) and heteroaryl containing substrates (**1h** and **1i**) at the γ-position and substrates with a primary alkyl at the β-position (**1j** and **1k**) were appropriate for the reaction as well. When the steric bulkiness of the β-substituent was increased to isopropyl (**1l**) and phenyl (**1m**), the efficiency of the process was lower than that of kinetic resolution (Scheme 1); isopropyl and phenyl substituted substrates yielded the reduced product in ~50% yield and high ee, but the remaining substrates were racemized (0–9% ee) by DBU.



Scheme 2. Substrate scope. [a] For this, 14% inseparable **1i** was co-eluted.



Scheme 3. Proposed catalytic cycle.

A proposed catalytic cycle for DKR of butenolides via copper-catalyzed 1,4-hydroboration using pinacolborane in the presence of an amine base is shown in Scheme 3. The successful reaction featured *in-situ* generation of Cu-H from the CuTC precursor and pinacolborane in the absence of an alkoxide base, racemization of *rac*-**1a** via amine, and selective 1,4-hydrocupration of (*R*)-**1a**.

In conclusion, we successfully achieved CuH-catalyzed 1,4-hydroboration of β,γ-disubstituted butenolides with pinacolborane via dynamic kinetic resolution. The new catalytic system uses a highly enantioselective copper-Ph-BPE catalyst, mild reaction conditions, and operational simplicity using an amine base and pinacolborane reagent. Extension of this process to other types of compounds is underway.

Experimental Section

General Procedure for Copper-Catalyzed Dynamic Kinetic Resolution of Butenolides with Pinacolborane; Pinacolborane (87.1 μL, 0.6 mmol) was added to a mixture of CuTC (2.8 mg, 0.015 mmol), and (*S,S*)-Ph-BPE (7.6 mg, 0.015 mmol) in THF (0.5 mL) in a Schlenk tube, and stirred for 15 min under an atmosphere of nitrogen. Racemic substrate *rac*-**1** (0.3 mmol) in THF (0.5 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (49.6 μL, 0.33 mmol) were added to the reaction tube. The reaction mixture was stirred at room temperature for 24 h and monitored by TLC and GC. After that, the reaction mixture was quenched with water. The aqueous layer was extracted with diethyl ether (3×10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by silica gel chromatography.

Acknowledgements

This research has been supported by grants from the National Research Foundation of Korea (NRF) (2019R1A2C2005706 and 2019R1A4A2001440).

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10.1002/adsc.202001353

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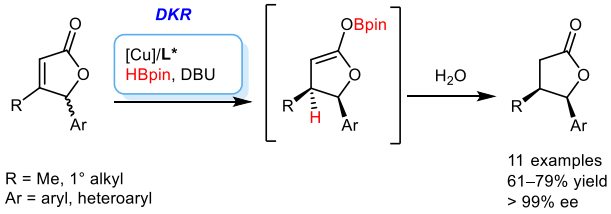

R = Me, 1° alkyl
Ar = aryl, heteroaryl

11 examples
61–79% yield
> 99% ee