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Dynamic Kinetic Resolution of Biaryl Lactones via a Chiral Bifunctional Amine Thiourea-Catalyzed Highly Atropo-enantioselective Transesterification

Chenguang Yu,[†] He Huang,[†] Xiangmin Li,[†,‡] Yueteng Zhang,[†] and Wei Wang*[,†,‡]

[†]Department of Chemistry & Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States
[‡]Shanghai Key Laboratory of New Drug Design, School of Pharmacy, and State Key Laboratory of Bioengineering Reactor, East China University of Science & Technology, Shanghai 200237, China

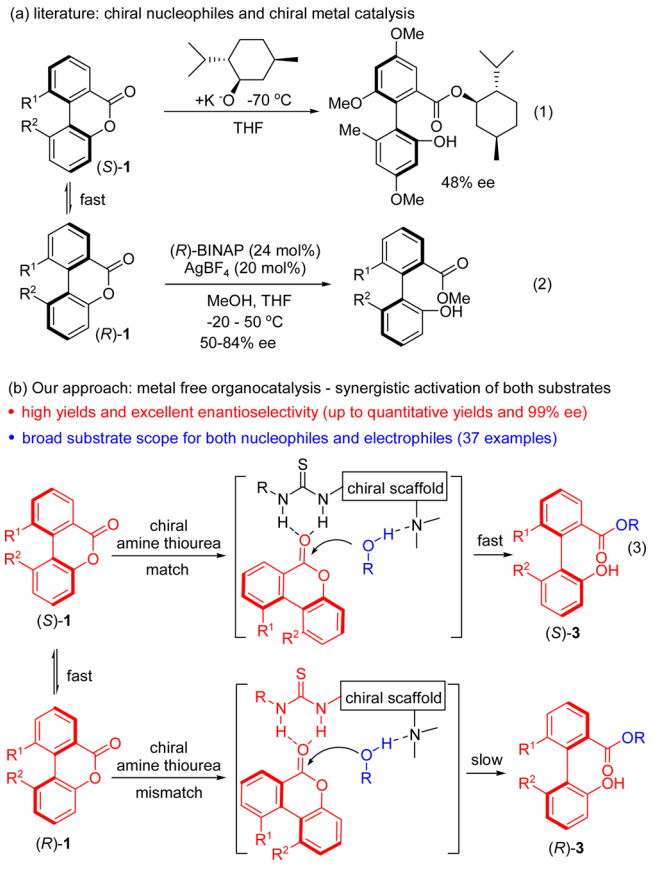
Supporting Information

ABSTRACT: A solution to the unmet synthetic challenge of achieving highly atropo-enantioselective transesterification of Bringmann's lactones has been realized, employing a chiral bifunctional amine thiourea as promoter. The synergistic activation of the lactones and alcohols/phenols by the respective thiourea and amine groups is crucial for achieving the highly enantioselective, high-yielding dynamic kinetic resolution process. This protocol gives highly optically pure, axially chiral biaryl compounds with a broad substrate scope under mild reaction conditions.

Dynamic kinetic resolution (DKR)[1] provides an unrivaled power over traditional kinetic resolution (KR)[2] in asymmetric synthesis, as it offers the capacity to convert both enantiomers of a racemic mixture into an enantioenriched product. Impressive progress has been made for catalytic DKR of compounds containing stereogenic centers.[3] By contrast, there are only a handful of examples reported regarding the synthesis of axially chiral compounds through catalytic DKR approaches, despite their prevalence and importance in bioactive molecules[4] and catalysis.[5] The general strategy employs catalytic atroposelective functionalization of configurationally labile biaryls to increase restriction to rotation in biaryl products. Chiral transition-metal-catalyzed introduction of a sterically demanding moiety at the *ortho*-position of freely rotating, rapidly racemizing biaryls[6b,e,f] or configurationally stable biaryls[6a,c,d] has been elegantly developed by the groups of Hayashi, Murai, Stoltz and Virgil, Fernández and Lassaletta, Colobert, and You.[6] However, the seminal work in organocatalytic DKR of racemic biaryls was only recently published by Miller with a tripeptide-promoted atroposelective electrophilic *ortho*-bromination reaction.[7,8]

DKR of configurationally labile biaryl lactones, developed by Bringmann, has proved to be a powerful approach to chiral biaryl compounds (Scheme 1, eq 1).[3a,4a,9] Notably, the chiral products have found broad applications in total synthesis of a number of challenging axially chiral natural products, such as korupensamine A and B,[10a] knipholone,[10b,c] mastigophorene A,[10d] and benanomicin B.[10e] Therefore, optically enriched biaryl products (>90% ee) are highly valuable for asymmetric total synthesis. However, achieving highly atropo-enantioselective DKR of Bringmann's lactones presents a long-standing challenge in synthesis, despite more than 20 years' effort by Bringmann and Yamada and others.[3a,4a,9,11,12] Diastereoselective transesterification of lactones with alcohols represents a straightforward approach to chiral biaryls but has had limited success so far. Chiral (+)-menthol-derived potassium alcoholate as chiral nucloephile gave the best result, with 48% ee (Scheme 1, eq 1, asymmetric transamidation giving better enantio-

Scheme 1. Reported Asymmetric and Proposed Chiral Bifunctional Amine-thiourea-Catalyzed Transesterification of the Bringmann's Lactones



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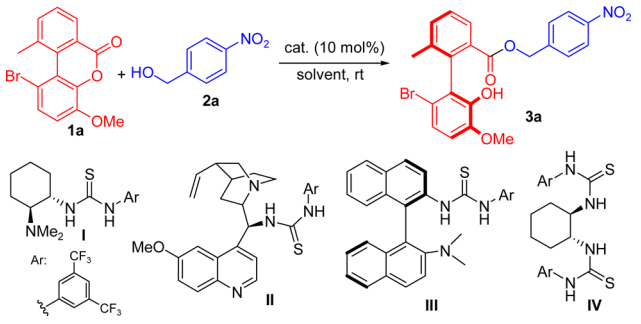
selectivity (86% ee)).[13] An asymmetric catalytic version using methanol as nucleophile by a chiral BINAP silver complex delivered moderate enantioselectivity (50−84% ee, Scheme 1, eq 2).[14] Clearly, a new catalytic strategy capable of promoting DKR of Bringmann's lactones with a high level of enantioselectivity (>90% ee) and a broad scope is urgently needed to streamline the synthesis of the privileged axially chiral biaryls.

Bifunctional chiral amine thioureas have demonstrated great versatility and selectivity to facilitate many transformations, attributed to their capacity for synergistic dual acid and base activation.[15] The effective activation mode and our experience in this area[16] inspired us to explore them for the DKR of the challenging Bringmann's lactones (Scheme 1, eq 3). We envisioned that thiourea activated the strained lactone, while the amine interacted with the hydroxyl group of an alcohol and directed the nucleophilic attack of the activated ester in a cooperative, atropo-enantioselective manner. Herein, we disclose the results of the investigation, leading to the first example of a metal-free quinine-derived thiourea-promoted atropo-enantioselective transesterification of Bringmann's lactones. Notably, this protocol is operated under very mild conditions and delivers axially chiral biaryl products in high yields and with excellent enantioselectivities (up to quantitative yields and 99% ee). Moreover, the process shows a much broader substrate scope than that of previous studies.[13,14] A variety of alcohols, including aliphatic alcohols and even phenols, perform very well. Moreover, biaryl lactones with a broad range of substituent patterns are efficienty transformed to chiral biaryl products.

We commenced our investigation by examining the reaction of biaryl lactone **1a** with 4-nitrobenzylic alcohol **2a** (Table 1).

Table 1. Exploration and Optimization[a]



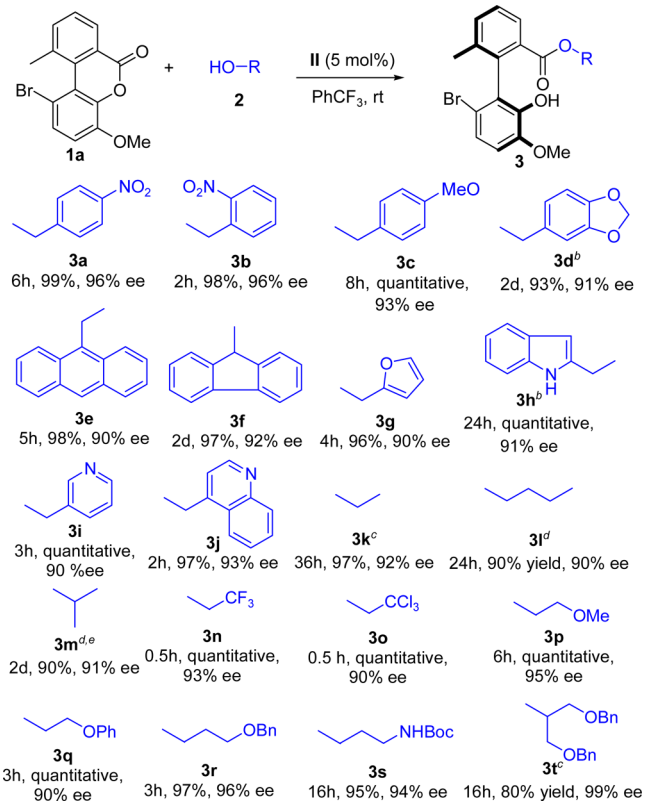
entry	cat.	solvent	t (h)	yield[b] (%)	ee[c] (%)
1	none	CH_2Cl_2	12	0	
2[c]	**I**	CH_2Cl_2	2	95	89
3	**II**	CH_2Cl_2	3	98	95
4	**III**	CH_2Cl_2	24	24	31
5	**IV**	CH_2Cl_2	24	0	
6	**II**	toluene	1.5	99	93
7	**II**	CF_3Ph	0.5	98	95
8	**II**	$CHCl_3$	1.5	99	94
9	**II**	xylene	1.5	91	94
10[d]	**II**	**CF_3Ph**	**6**	**99**	**96**
11[e]	**II**	CF_3Ph	72	61	96

[a]Unless specified, the reaction was carried out with 0.1 mmol of **1a** and 0.12 mmol of **2a** in 1.0 mL of a solvent with x mol% catalyst, stirred at rt for a specified time. [b]Isolated yields for both isomers. [c]Determined by chiral HPLC analysis (Chiralcel AS-H). [d]5 mol% catalyst used. [e]1 mol% catalyst used.

No reaction happened without a catalyst, indicating that a promoter is essential for effective transesterification (entry 1). Indeed, Takemoto's catalyst **I** was capable of producing the desired product **3a** in 95% yield and with 89% ee within 1 h (entry 2). Among the commonly used amine thioureas probed, Soós's quinine thiourea **II** proved to be a superior facilitator for this process, giving **3a** in 98% yield and with 95% ee in 3 h (entry 3). The power of the synergistic activation specifically by a bifunctional amine and thiourea was demonstrated when no reaction proceeded with either triethylamine or bis(thiourea) catalyst **IV** (entry 5). Further examining the parameters of solvents (entries 3 and 6−9) and catalyst loading (entries 10 and 11) revealed the optimal reaction conditions of trifluorotoluene as medium and 5 mol% of **II**.

With the optimized condition in hand, the scope of the process was explored (Scheme 2). Benzyl alcohols with

Scheme 2. Alcohols as Nucleophiles[a]



[a]Unless specified, see Table 1, footnote *a*, and SI; yields refer to isolated, ee determined by chiral HPLC. [b]−10 °C. [c]2.0 equiv of alcohol. [d]20.0 equiv of alcohol. [e]15 mol% **II**.

electron-withdrawing (**2a**, **2b**) or -donating substituents (**2c**, **2d**) gave the desired products in excellent yields and with excellent enantioselectivities (93% to quantitative yields, 91−96% ee). More sterically demanding 9-anthracenemethanol (**2e**) and diaryl-substituted methanol **2f** were well tolerated. Moreover, heteroaromatic rings including furan (**2g**), indole (**2h**), pyridine (**2i**), and quinoline (**2j**) proved to be valid substrates. Besides benzyl alcohols, simple aliphatic alcohols such as EtOH, *n*-BuOH, and *i*-PrOH, which gave low enantioselectivity in Yamada's study,[13] delivered high yields of highly enantioenriched **3k**−**m** (97, 90, and 90% yields, and 92, 90, and 94% ee, respectively). More acidic trifluoro- (**2n**) and trichloroethanol (**2o**) reacted much faster (within 0.5 h) but

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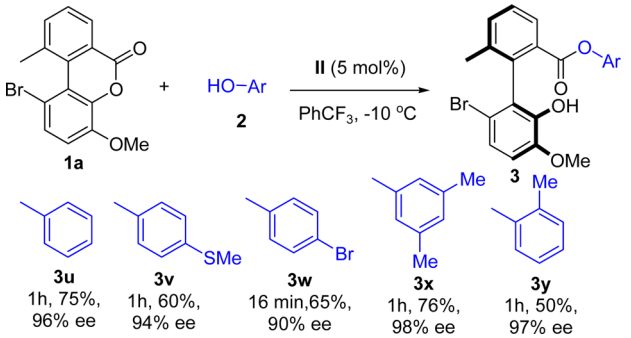
without deteriorating enantioselectivity, presumably as a result of easy deprotonation of the OH group by the amine. 2-Methoxyethanol (**2p**) was found to give higher enantioselectivity in shorter time than ethanol (95% ee, 6 h vs 92% ee, 36 h), which may be ascribed to the oxygen atom acting as an additional binding site with the catalyst and the increased acidity of alcohols by inductive effect of the oxygen. In contrast, 2-phenoxyethanol (**2q**) gave lower enantioselectivity (90% ee), maybe due to weaker binding ability of the phenoxyl. Excellent yields (95−97%) and enantioselectivities (94−96%) were also found for other functionalized alcohols, 3-benzyloxy-1-propanol (**2r**) and N-substituted alcohol **2s**. It is noted that 1,3-dibenzyloxy-2-propanol (**2t**), with two oxygen substituents, further improved enantioselectivity (99% ee) for **3t**.

The synthesis of axially chiral phenolic esters from Bringmann's lactones is more challenging due to the weaker nucleophilicity of phenols and their vulnerable racemization via reversible lactonization. We found that the sensitive chiral phenolic esters could be prepared by using this protocol but have to balance selectivity and reactivity. Prolonging reaction time could increase yields but caused racemization of the products. We managed to achieve high to excellent enantioselectivities (90−98% ee) and good yields (50−76%) for phenols bearing electron-neutral (**2u**), -donating (**2v**, **2x**, and **2y**), and -withdrawing substituents (**2w**) when the reaction was performed at −10 °C with controlled short reaction time (Scheme 3). It is noteworthy that, although great success has

Scheme 3. Phenols as Nucleophiles[a]

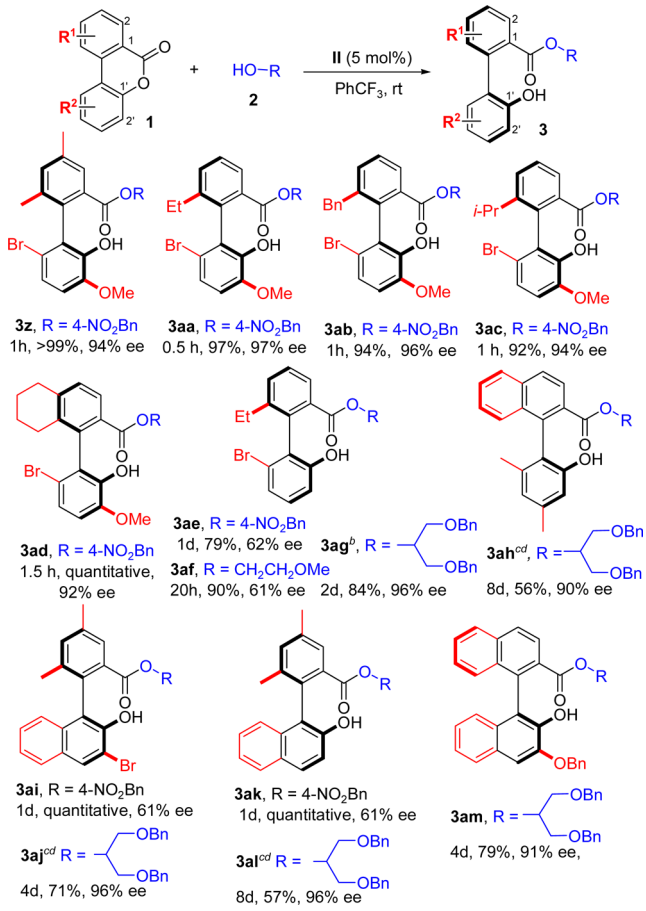


[a]Unless specified, see Table 1, footnote *a*, and SI; yields refer to isolated, ee determined by chiral HPLC.

been achieved for asymmetric transesterification of biaryl lactones with alcohols, disappointing results were obtained in our attempts with nitrogen-centered nucleophiles. Aniline and tosylamide did not deliver any transamidation product, while piperidine reacted with **1a** smoothly but gave 0% ee.

After probing the scope and understanding the influence of alcohols/phenols on the reaction, we next investigated the tolerance of biaryl lactones (Scheme 4). It appears that the variation of substituents on the carbonyl-containing phenyl ring does not show any influence, producing **3z**, **3aa**, **3ab**, **3ac**, and **3ad** in excellent yields and with excellent ee (92%-quantitative yields, 92−97% ee). Nonetheless, removal of the 2′-methoxyl substituent on the phenolic parts causes dramatic decreases in both yield and ee (**3ae**, 79%, 62% ee vs **3aa**, 97%, 97% ee). It is believed that the methoxyl substituent in biaryl lactone may provide an additional binding site with the catalyst to increase alcohol's differentiation in attack trajectory. We observed alcohols could affect enantioselectivity. Therefore, different

Scheme 4. Scope of Biaryl Lactones[a]



[a]Unless specified, see Table 1, footnote *a*, and SI; yields refer to isolated, ee determined by chiral HPLC. [b]2.0 equiv of alcohol. [c]10 equiv of alcohol. [d]15 mol% of **II**.

alcohols were probed, including 2-methoxyethanol (**2p**), possessing an additional oxygen atom that provided an additional binding site for boosting enantioselectivity, but a similar result was found for **3af**. Pleasingly, 1,3-dibenzyloxyl-2-propanol (**2t**) could give a dramatic increase of enantioselectivity (96% ee) and high yield (84%) for **3ag**. Moreover, importantly, **2t** served as a general nucleophile to give high levels of enantioselectivity (90−96% ee) for **3ah**, **3aj**, **3al**, and **3am** without the methoxyl group on the 2′ position. In addition, we also conducted comparison studies with **2t** and **2a**. Similar enhancements were also observed, such as **3aj**, 96% ee vs **3ai**, 61% ee and **3al**, 96% ee vs **3ak**, 61% ee.

The protocol can be easily scaled up to a gram scale using a lower catalyst loading (2 mol%) at a higher concentration (1.0 M) affording 1.167 g of **3a** in nearly quantitative yield and excellent ee (95%, Scheme 5, eq 1). Alcohol **4** can be smoothly attained by $LiAlH_4$ reduction in 93% yield and without erosion of optical purity. Furthermore, a useful chiral aminophenol ligand **6**[17] can be prepared from product **3al** via DIBAL-H-mediated reduction (Scheme 5, eq 2). Therefore, the absolute configuration of transesterification products **3** is confirmed by the comparison of the optical rotation of **5** with the reported data.[11a]

Driven by the unmet synthetic issue in atropo-enantioselective transesterification of Bringmann lactones, we have developed a new chiral bifunctional amine thiourea organo-

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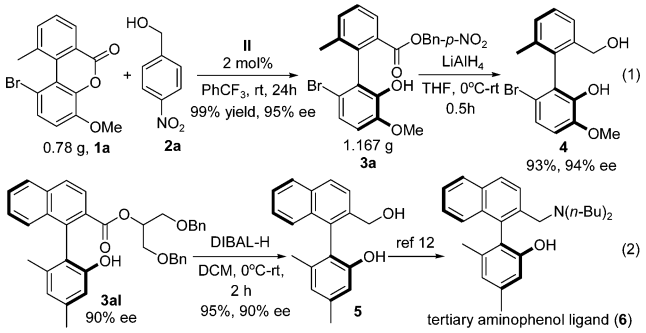
Scheme 5. Gram Scale Synthesis and Synthetic Elaboration of the Transesterification Products



catalyst promoted highly enantioselective approach to axially chiral biaryl compounds with a broad substrate scope under mild reaction conditions. The higher reaction efficiency attributes to a distinct synergistic activation mode from previous reported monoactivation methods. The new strategy will streamline the synthesis of the privileged axially chiral biaryls. Application of the axially chiral products in synthesis of natural products and new chiral molecules is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03609.

Experimental details and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*wwang@unm.edu

Notes

The authors declare no competing financial interest.

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