Atroposelective Synthesis of Axially Chiral Thiourea and Imides by NHC-Catalyzed Desymmetrizative Amidation

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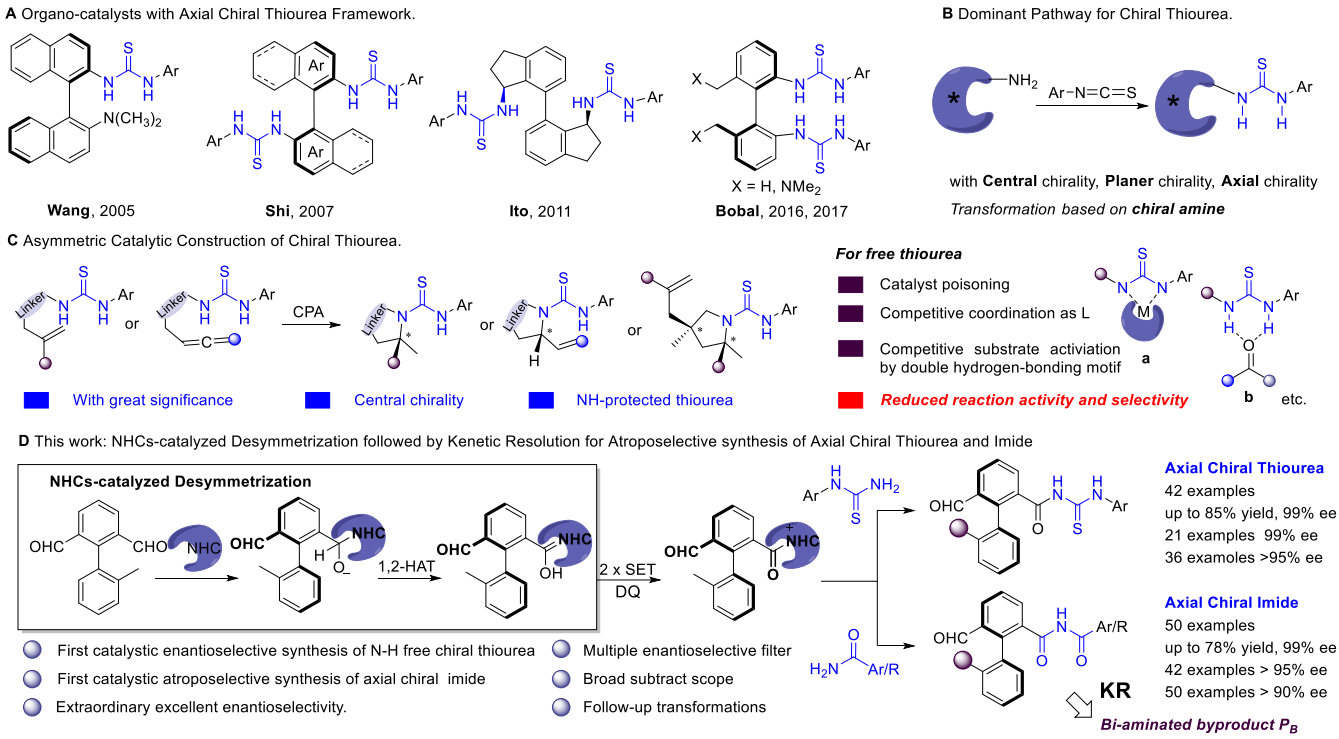
Abstract: Chiral thiourea, with a double hydrogen-bonding motif, emerged as attractive structural templates for asymmetric catalysis. Despite the significance, synthesis of enantioenriched thiourea predominantly relies on the nucleophilic addition of a chiral amine to isothiocyanate; catalytic synthesis of NH-free thiourea is highly desirable, albeit a formidable challenge. We herein describe NHCs-catalyzed desymmetrizative amidation of axially biaryl dialdehydes, providing structurally diversified axially chiral thiourea and imides. Sequential kinetic resolution improves the enantioenrichment of the desymmetrization product, dramatically expanding the range of applicable substrates. This strategy features a broad subtract scope and extremely excellent enantioselectivity. NHCs-catalyzed desymmetrizative amidation of axially prochiral biaryl dialdehydes provides modular platforms for synthesizing challenging axially chiral thiourea, imines, and derivatives.

Thiourea derivatives[1], such as carbonyl thiourea[2], found widespread applications in natural products, drug design, agricultural chemicals, and antibacterial agent owing to their unique bioactive activities. Chiral thiourea derivatives[3], with double hydrogen-bonding motif, emerged as important structural templates for the organocatalytic design to activate carbonyl groups and related compounds through weak hydrogen-bond interaction[4]. In this domain, as pioneered by Wang[5] and Shi[6] group, axially chiral thiourea catalysts[7] received increasing attention in asymmetric catalysis in recent years (Scheme 1A), and chiral thiourea with different backbone were developed for efficient asymmetric transformations, including Michael addition, Morita-Baylis-Hillman reaction, Henry reaction, etc. Enantioenriched thiourea scaffold synthesis has been a long-standing assignment in organic chemistry, and the development of efficient methods for it is crucial. The dominant pathway for achieving enantioenriched thiourea scaffolds is through the nucleophilic addition of a chiral amine to isothiocyanate, resulting in the formation of thiourea with central, planar, or axial chirality (Scheme 1B). Notable catalytic approaches were state-of-the-art intermolecular hydroamidation of alkenes, or allenes developed by Liu and coworkers[8], enables the efficient construction of NH-protected thiourea (Scheme 1C). Despite the significance, enantioselective catalytic synthesis of NH-free thiourea has never been reported yet, which might be obstructed by catalyst poisoning or competitive coordination (metal-catalytic system, Scheme 1Ca) as well as competitive substrate activation (organo-catalytic system, Scheme 1Cb), resulting in reduced reaction activity and selectivity. The prospect of developing a novel catalytic approach to achieving efficient synthesis of highly enantioenriched NH-free thiourea from easily accessible starting materials is extremely attractive, albeit a formidable challenge.

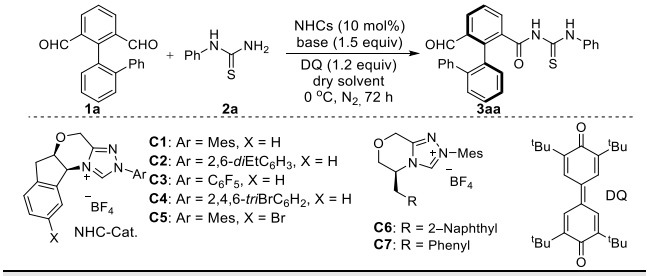
Desymmetrization, the process of breaking the symmetry of meso or prochiral molecules, is an attractive and powerful tool for achieving enantioenriched complex chiral compounds.[9] Prochiral dialdehydes, which could serve as substrates for desymmetrization,[10] have two reaction sites and are susceptible to over-functionalization, leading to the formation of bifunctionalization byproducts (P_B). Undoubtedly, in the scenario of desymmetrization followed by matched kinetic resolution could amplifying stereoinduction *via* the accumulation of P_B, resulting in extraordinary high theoretical *ee* (> 99%).

On the other hand, N-heterocyclic carbenes catalysis (NHCs) received increasing attention in organic synthesis and asymmetric catalysis owing to its unique reactivity in activating carbonyl[11] groups and transfer acyl[12] groups. NHCs-catalyzed transformations inject fresh vitality for constructing axial chiral compounds via (dynamic) kinetic resolution[13], desymmetrization[10d,14], or atroposelective cyclization[15] strategy. We speculated that NHCs-catalyzed desymmetrization of axially prochiral dialdehydes[10d] exhibit high reactivity and selectivity, might provide an opportunity for challenging asymmetric coupling with weakly nucleophilic thiourea. As our continued efforts in NHC catalysis[16] and asymmetric catalysis[10d,17], we now report NHCs-catalyzed desymmetrizative amidation of axially biaryl dialdehydes employing thiourea as amidation source, leading to the unprecedented enantioselective catalytic synthesis of NH free thioureas (Scheme 1D). The amidation reagents can be extended to amide. While there have been reports of elegant sporadic catalytic construction of axially chiral biaryl amides[15d, 18], to the best of our knowledge, our approach represents the first catalytic synthesis of axially chiral biaryl imides. Additionally, the chiral amplification phenomenon can significantly improve the enantioenrichment of the desymmetrization product. This means that a high level of enantioinduction for the desymmetrization step may not be necessary, which has dramatically expanded the range of applicable substrates.



Scheme 1. NHCs-catalyzed desymmetrizative amidation and sequential kinetic resolution for axial chiral thiourea and imide.

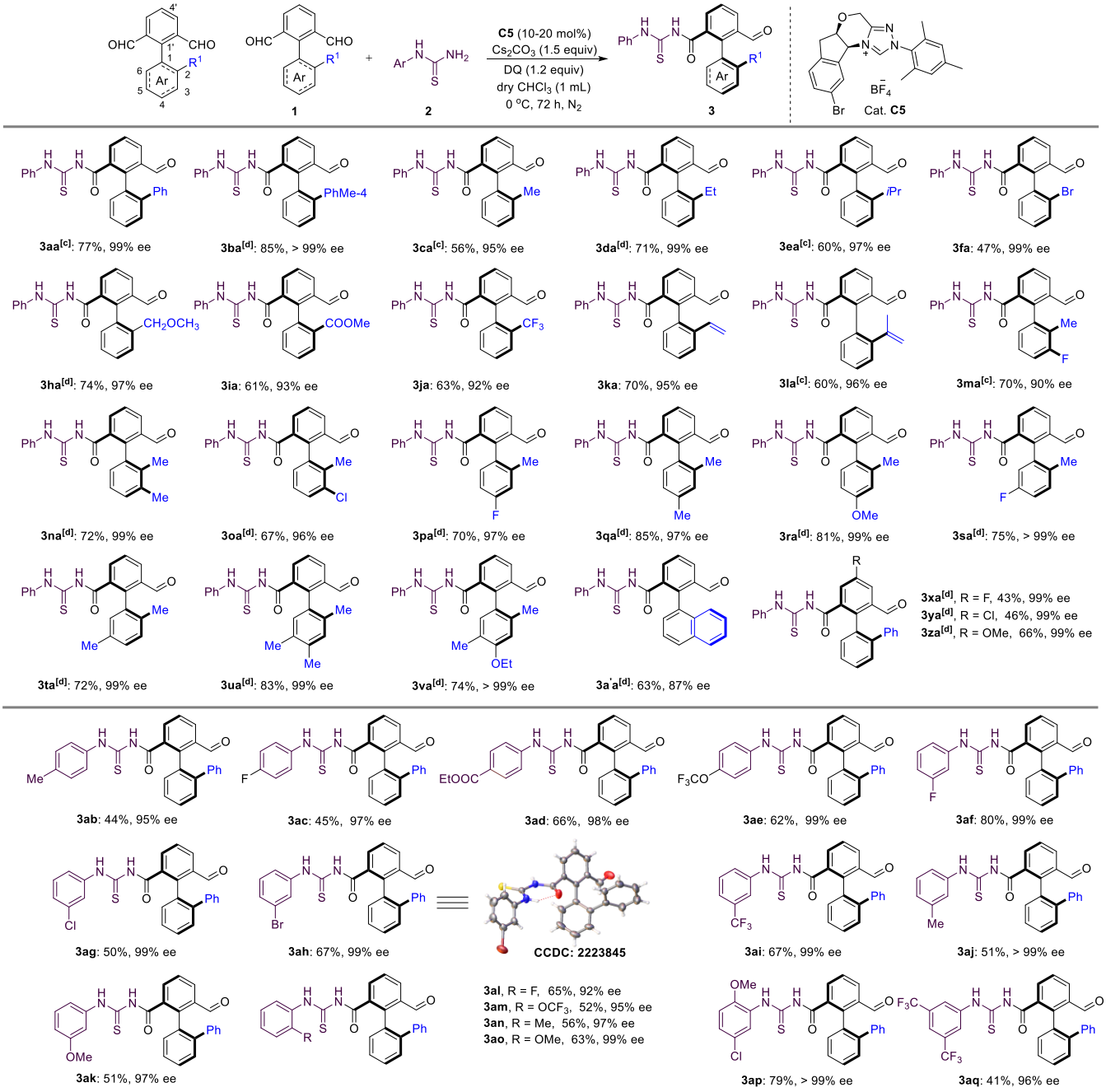
Table 1 Optimization of the reaction conditions[a]



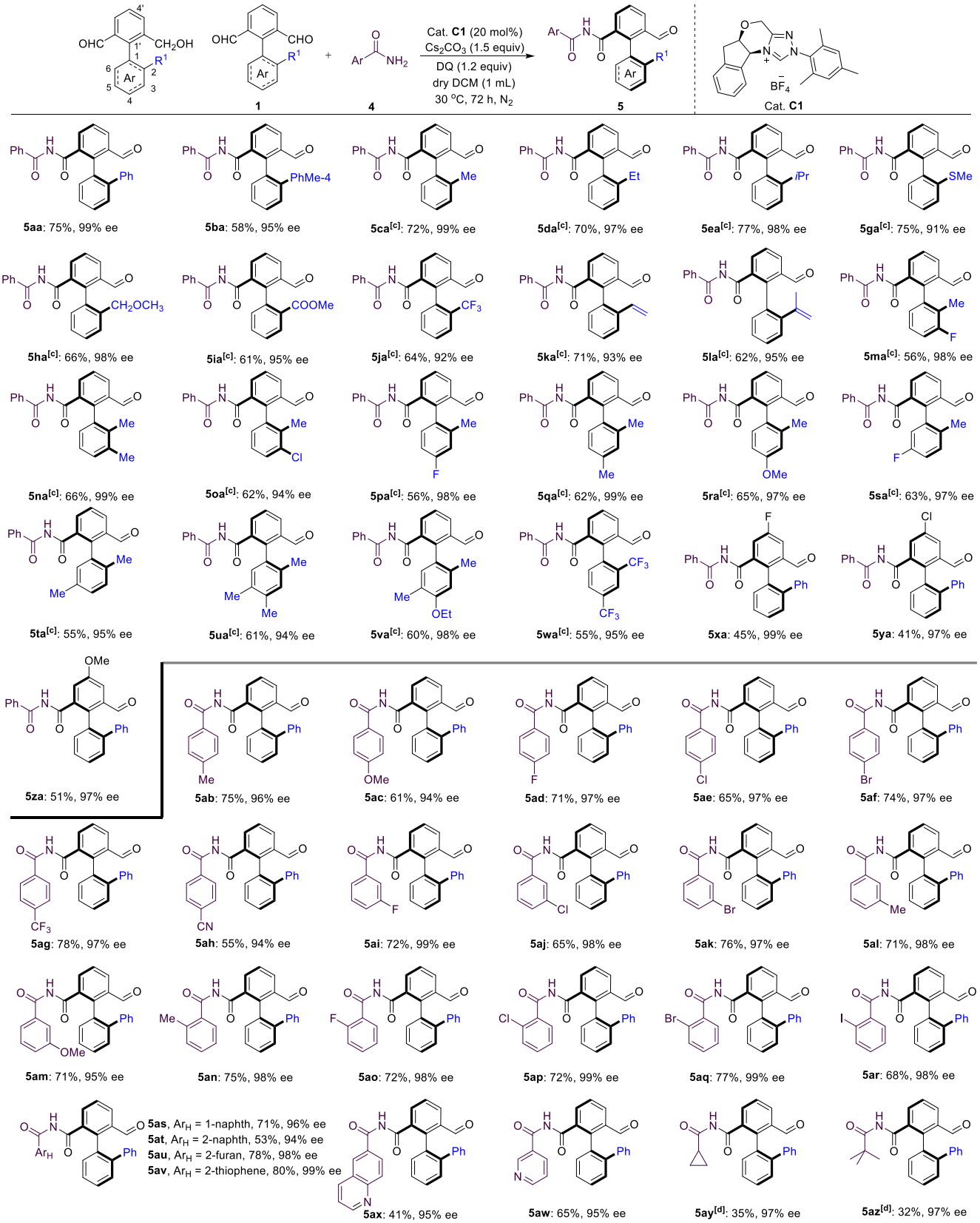
Entry	NHC Cat.	Solvent	Base	Conv. (%)	**3aa** (%) Yield	*ee*
1	**C1**	DCM	Cs_2CO_3	51	48	96
2	**C2**	DCM	Cs_2CO_3	30	22	75
3	**C3**	DCM	Cs_2CO_3	trace	trace	--
4	**C4**	DCM	Cs_2CO_3	23	16	93
5	**C5**	DCM	Cs_2CO_3	70	52	98
6	**C6**	DCM	Cs_2CO_3	41	33	58
7	**C7**	DCM	Cs_2CO_3	20	19	12
8	**C5**	THF	Cs_2CO_3	20	15	96
9	**C5**	TBME	Cs_2CO_3	20	10	91
10	**C5**	DCE	Cs_2CO_3	49	43	94
11	**C5**	**$CHCl_3$**	**Cs_2CO_3**	**84**	**79 (77)**	**99**
12	**C5**	Toluene	Cs_2CO_3	30	11	89
13	**C5**	EtOAc	Cs_2CO_3	25	20	93
14	**C5**	$CHCl_3$	K_2CO_3	30	24	99
15	**C5**	DCM	K_3PO_4	25	16	99
16	**C5**	DCM	NaH	76	75	98

[a] Conditions: **1a** (0.1 mmol), **2a** (3.0 equiv), NHCs. (10 mol%), base (1.5 equiv) and DQ (1.2 equiv), solvent (1.0 mL), 0 °C, N_2 atmosphere, 72 h. Yields were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture employing CH_2Br_2 as the internal standard; isolated yield was provided in parentheses. *ee* was determined by chiral-phase HPLC analysis.

We commenced our investigation by the reaction of axial prochiral dialdehydes **1a** with aryl thiourea **2a** employing Cs_2CO_3 as base and saminoindanol-derived *N*-Mes substituted **C1** as *pre*-catalyst in the dichloromethane (DCM). Fortunately, desired enantioenriched axial chiral thiourea was monitored by 48% yield and 96% *ee* (Table 1, entry 1). This proof-of-principle result greatly encouraged us to screen other chiral NHCs further (entries 2–7). *N*-mesityl substituent seems valuable for reactivity and selectivity; **C2**-**C4** with bulkier or electron-deficient aryl group gives unsatisfied results (entries 2-4). Bromo-substituted **C5** gives slightly improved yield and *ee* (entry 5). L-phenylalanine-derived triazolylidenes **C6** and **C7** provide lower yield and reduced levels of enantioselectivity (entries 6-7). A range of solvents was screened (entries 8-13) for this amidation reaction, and generally high enantioselectivities (almost > 90% *ee*) were afforded; among them, $CHCl_3$ was the best choice, and **3aa** could isolated in 77% yield, 99% ee (entry 11). The base screening revealed that the reactivity of amidation was significantly reduced by employing weak bases such as K_2CO_3 or K_3PO_4; however, it did not affect the enantioselectivity. The NaH gives similar results as Cs_2CO_3; considering the operation simplicity and functional group tolerance, conditions in entry 11 were identified as optimized reaction conditions for evaluating substrate scope.



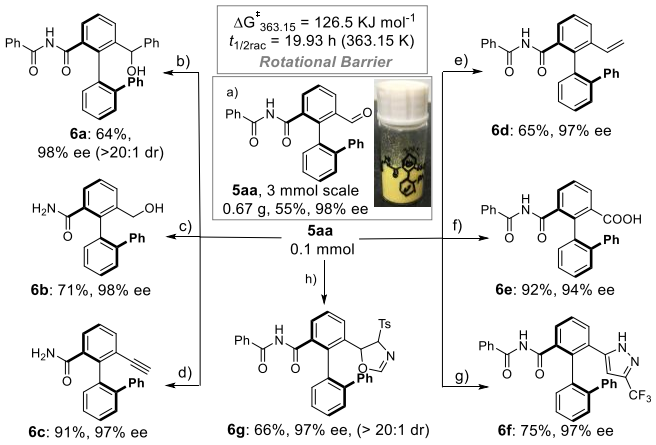
Scheme 2. Substrate scope for catalytic synthesis of axially chiral thiourea.[a,b] [a] Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **2** (0.3 mmol), **C5** (20 mol%), DQ (1.2 equiv), Cs_2CO_3 (1.5 equiv), and dry $CHCl_3$ (1.0 mL) at 0 °C under N_2 atmosphere for 72 h. [b] Isolated yield, *ee* was determined by chiral-phase HPLC analysis. [c] Reactions were carried out with **C5** (10 mmol%). [d] Reactions were carried out with **C5** (15 mmol%)



Scheme 3. Substrate scope for catalytic synthesis of axially chiral imide.[a,b] [a] Unless otherwise noted, all the reactions were carried out with **1** (0.1 mmol), **4** (0.3 mmol), NHC-1(20 mol%), DQ (1.2 equiv), Cs_2CO_3 (1.5 equiv), and dry DCM (1.0 mL) at 30 °C under N_2 atmosphere for 72 h. [b] Isolated yield, *ee* was determined by chiral-phase HPLC analysis. [c] Reactions were carried out with NHC-1 (10 mmol%). [d] Reactions were carried out with **4** (5.0 equiv)

With the optimized conditions in the hand, the scope and limitation for the synthesis of axially chiral thiourea was then investigated. Firstly, the limitation of the blocking group was firstly investigated by the coupling with phenyl thiourea **2a**. Switching the 2-phenyl group to 2-(*4*-MeC_6H_4) has no effect to selectivity and reactivity, delivering **3ba** in 85% yield and > 99% ee in 15 mol% catalyst loading. Alkyl group inculding minimal methyl, ethyl, and isopropyl have been proven to be effective, generating desired thiourea (**3ca**-**3ea**) in moderate yields and excellent enantioselectivity (>95%). Bromine (**1f**), methoxymethyl (**1h**), ester carbonyl (**1i**), trifluoromethyl (**1j**) groups can be introduced in to the ortho-position of axially prochiral dialdehydes, with the corresponding products (**3fa, 3ha**-**3ja**) afforded in moderate to good yields and high optical purities. Moreover, alkenyl groups were also tolerated, as identified by the formation of **3ka** (70%, 95% ee) and **3la** (60%, 96% ee). Induction of atroposelectivity is always significantly affected by the steric hindrance of blocking groups, which is why bulky groups are always required. Nonetheless, it is worth mentioning that our system exhibits exceptional tolerance towards blocking groups, even the challenging ones such as methyl (**3ca**), alkenyl (**3ka** and **3la**), and other groups. We fixed the methyl group as the blocking group and evaluated different substrates with electron-donating groups (such as alkyl and alkoxy) or fluorine groups at different positions of the aryl ring of **1**. Those prochiral dialdehydes with *di*substituted (**3ma**-**3ta**), or *tri*-substituted (**3ua**, **3va**) aryl rings all reacted smoothly with **2a** with good yields (67-83%) and excellent enantioselectivity control (up to >99 % *ee*). Naphthalene ring substituted dialdehydes were also suitable (**3a'a**), with slightly reduced yield and *ee*. Finally, the substituent effect of dialdehydes for 4' position was investigated, and desired products **3xa**-**3za** was isolated in acceptable yields and 99% ee. Then we explored the reaction scope of the aryl thiourea **2** by the coupling with **1a**. Both electron-donating alkyl (**3ab**, **3aj**, **3an**), alkoxy (**3ak**, **3ao**); halogen (**3ac**, **3af**, **3al**); and electron-withdrawing ester carbonyl (**3ad**), trifluoromethyl (**3ai**), trifluoromethoxy (**3ae**, **3am**) substituents can be introduced into different position on the aryl ring of thiourea, with the corresponding axially chiral thiourea in moderate to good yield (44-80%) and outstanding enatioinrichment (in allmost cases > 95%). The absolute configuration of **3ah** was determined by X-Ray studies (CCDC 2223845)[19]. For *ortho*-substituted aryl thiourea, acceptable yields and excellent *ee* was observed for **3al**-**3ao**, indicating the tolerance of steric hindrance of thiourea. 2,4-disubstitued aryl thiourea were also tolerated and generating **3ap** in 79% yield and > 99% *ee*. Finally, 3,5-*di*-CF_3 substituted aryl thiourea, frameworks prevalent in chiral catalysts, could also undergo acylation smoothly, forming **3aq** in acceptable yield and 96% ee. It is worth noting the remarkable enantioselectivity and wide-ranging functional group and blocking group compatibility in our asymmetric acylation of thiourea.

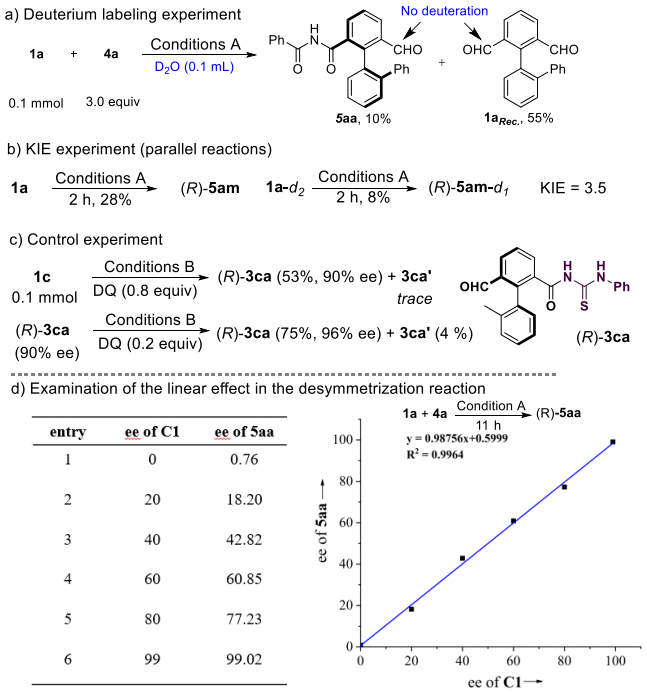
Besides the thiourea, the scope with respect to easy to access amide were also evaluated. The atroposelective acylation of amides with axially prochiral biaryl dialdehydes could lead to an unprecedented catalytic synthesis of axially chiral biaryl imines. The successful coupling of dialdehyde **1a** and benzamide **4a** was achieved by the employment of **C1** (20 mol%) as pre-catalyst, Cs_2CO_3 (1.5 equiv) as base, DQ (1.2 equiv) as oxidant in dry DCM under N_2 atmosphere at 30 ^oC for 72 hours (Details for optimization see SI). This resulted in the production of the desired axially chiral imine **5aa** in a 75% yield and 99% ee. Various blocking groups, such as aryl (**5aa**, **5ab**), alkyl (**5ca**-**5ea**), thiomethyl (**5ga**), methoxymethyl (**5ha**), ester carbonyl (**5ia**), trifluoromethyl (**5ja**), alkenyl (**5ka**, **5la**) substituent at the 2-position of dialdehydes were successfully applicated in this atroposelective C-H amidation, affording corresponding axial chiral imines in ranging from 58-77% yields and excellent optical purities (up to 99% ee). The dialdehydes that bear disubstituted or trisubstituted arenes with a fixed methyl group at the 2-position have been proven to be versatile starting materials for amidation. These dialdehydes delivering corresponding axially chiral imines **5ma**-**5va** with moderate yield (56-66%) and good enantioenrichment (94-99% ee). Dialdehyde bearing 2,4-*di*-CF_3 substituted aryl ring did not affect the reactivity and selectivity, as evidenced by the 51% yield and 97% ee of **5wa**. Next, the 4'-substituted dialdehyde with a fixed phenyl group at the 2-position was tested, which resulted in the production of desired axial chiral imines **5xa**-**5za** in wonderful *ee* and moderate yields. Moreover, the substitution pattern of the amide could also be varied successfully. Aryl amides bearing electron-donating, halogen, and electron-withdrawing groups at the *para*-position of the aryl ring could deliver **5ab**-**5ah** in 55-78% yield and 94-99% *ee*, indicating tolerance for electronic effects. Substituent at *meta*- or *ortho*-position nearly no effect to reaction efficiency and chiral induction, as identified by the formation of enantioenriched **5ai**-**5ar**. It is worth noting that the presence of halogens, particularly iodine (**5ar**) and bromine (**5af**, **5ak**, **5aq**) atoms, in aryl amides can offer ability for subsequent cross-coupling reactions, thus providing additional synthetic opportunities. This transformation was also applicable to amide bearing fused ring (**5as**, **5at**), electron-rich (**5au**, **5av**), or electron-deficient heteroarene (**5ax**, **5aw**). Finally, alkyl amides (**5ay**, **5az**) were also applied for this atroposelective amidation reaction and excellent enantioselectivity was observed, albeit with lower reactivity.



Scheme 4. Large-scale synthesis and follow-up transformations. Reaction conditions: a) **C1** (20 mol%), Cs_2CO_3 (1.5 equiv), DQ (1.2 equiv), dry DCM (0.1 M), 25 ^oC, N_2, 72 h; b) 1, PhMgBr (1.1 equiv), dry THF (0.1 M), 0 ^0C, 48 h, 2, H_3^+O; c) $NaBH_4$ (1.0 equiv), THF/CH_3OH = 3:1 (0.1 M), 0 ^oC, 12 h; d) P-(1-diazo-2-oxopropyl)-diMethylester (1.5 equiv), K_2CO_3 (2.0 equiv), MeOH (1 mL), rt. 3 h; e) $(PPh)_3P^-CH_3Br^+$ (1.2 equiv), ^{n}BuLi (1.2 equiv), dry THF (0.1 M), 0 ^0C, 30 min, then drop **3aa**, rt, 12 h; f) $NaClO_2$ (3.7 equiv), NaH_2PO_4 (5.0 equiv), 2-methylbut-2-ene (13.0 equiv), ^{t}BuOH (0.15 M), rt, overnight; g) $TsNHNH_2$ (1.2 equiv), 2-Bromo-3,3,3-trifluoropropene (2.0 equiv), DBU (3.0 equiv), PhMe (1 mL), 60 °C, 6 h; h) Tosylmethyl isocyanide (1.0 equiv), Cs_2CO_3 (2.0 equiv), DMF(0.05 M), 25 ^oC, N_2, 8 h.

Gram-scale synthesis and subsequent transformations were performed to further showcase the synthetic utilization of the desymmetrizing amidation system. At a 3.0 mmol scale, a gram-scale synthesis was conducted and yielding (R)-**5aa** in 55% (0.67 g) yield and 98% ee (Scheme 4a). The aldehyde group and imine group are highly versatile organic building blocks that allow for further transformations. **5aa** could undergo diastereoselective nucleophilic addition with PhMgBr (Scheme 4b), affording axial chiral secondary alcohols **6a** in 65% yield and 98% ee (> 20:1 dr). Axial chiral alcohols **6b** (71%, 98% ee) could obtained by the reduction of **5aa** by $NaBH_4$, and cascade C-N cleavage (Scheme 4c). Intriguingly, Seyferth-Gilbert homologation (Scheme 4d) or Wittig reaction (Scheme 4e) of **5aa** produced axially chiral biaryls containing alkynyl or alkenyl **6d** (65%, 97% ee) group. In the case of Seyferth-Gilbert homologation, the imine group was hydrolyzed to amide **6c** (91%, 97% ee). The oxidation of the aldehyde group generates valuable axial chiral carboxylic acid **6e** in 92% yield and slightly eroded ee (Scheme 4f). The aldehyde group underwent cascade annulation with $TsNHNH_2$ and 2-Bromo-3,3,3-trifluoropropene delivering pyrazole **6f** (Scheme 4g). **5aa** underwent cycloaddition with

tosylmethyl isocyanide delivering **6g** (66%, 97% ee) in excellent *dr* (Scheme 4h). The rotational barrier for the C-C bond in **5aa** was then investigated, and $\Delta G^{\neq}_{rac}$ = 126.5 KJ/mol, which corresponded to a half-life of 19.9 hours at 90 °C (*i*-PrOH). **5aa**'s configurational stability could result in a high degree of chiral retention in subsequent transformations. This methodology might provide a new avenue for the synthesis of axial chiral imide, amide, and other derivative.



entry	ee of C1	ee of 5aa
1	0	0.76
2	20	18.20
3	40	42.82
4	60	60.85
5	80	77.23
6	99	99.02

Scheme 5. Mechanistic studies and proposed mechanism.

We conducted a series of mechanism investigations to get insight into the reaction pathway. According to the deuterium exchange experiment, deuterium atoms were not introduced into the product or the recovered raw materials (Scheme 5A). This result suggests that the cleavage of aldehyde C-H bonds is irreversible under the reaction conditions. The kinetic isotope effect measurement was conducted by comparing the initial reaction rate of **1a** and **1a-*d*$_2$** in parallel reactions. The observed KIE was 3.5, which suggests that C-H bond cleavage may be involved in the rate-determining step. Since C-H bond cleavage is irreversible, the formation of BI intermediates via the condensation of aldehyde and NHC appears to be a rate- and enantio-determining step. Control experiments were conducted and, the *ee* of **3ca** could improve from 90% to 96% by over-functionalization. By sacrificing minor enantiomers generated in first desymmetrization step, the matched kinetic resolutions severed as efficient enantioselective fitter in enhancing enantioselectivity. Scheme 5d showed a linear correlation between the *ee* value of **C1** and product **5aa**. It can be inferred that only a single NHC is likely to be involved in the stereo-determining step, as the absence of nonlinear effect.

In summary, we have developed NHCs-catalyzed general and robust desymmetrizative amidation of readily accessible axially prochiral dialdehydes, leading to unprecedented catalytic synthesis of axially chiral thiourea and imines. Mechanistic studies indicate that transformation proceed *via* irreversible rate- and enantio-determination activation of aldehyde followed by oxidative C-N bond formation. Sequential kinetic resolution served as an efficient enantioselective filter, significantly enhanced the enantiomeric excess of the desymmetrization product. This approach broken the requirement of rigorous stereoselectivity induction for the desymmetrization step, which has dramatically expanded the range of applicable substrates. This strategy futures mild conditions, broad subtract scope (42 examples for axially chiral thiourea; 50 examples for axially chiral imides), and excellent enantioselectivity (up to 99% *ee*). The follow-up transformation highlighted the synthetic value of the amidation system as it enables direct access to versatile axially chiral biaryl compounds with minimal erosion of enantioselectivity. NHCs-catalyzed desymmetrization and functionalization of axially prochiral biaryl dialdehydes provide modular platforms for synthesizing challenging axially chiral thiourea, imines, and derivatives.

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Keywords: N-heterocyclic carbenes • axially chiral thiourea • axially chiral imine • desymmetrization • chiral amplification • amidation

[1] K. A. Agnew-Francis, C. M, Williams, *Chem. Rev.* **2020**, *120*, 11616-11650.

[2] a) M. A. Ibrahim, M. S. Mohd Yusof, N. Mat Amin, *Molecules*. **2014**, *19*, 5191-5204; b) T. Yun, T. Qin, Y. Liu, L. Lai, *Eur. J. Med. Chem*. **2016**, *124*, 229-236; c) H. Siddiqui, S. Shafi, F. Mukhtar, A. Ejaz, M. I. Choudhary. *Med. Chem*. **2018**, *14*, 508-515; d) Z. Li, W. Xin, Q. Wang, M. Zhu, H. Zhou. *Eur. J. Med. Chem*. **2021**, *217*, 113319; e) W. W. Ni, H. L. Fang, Y. X. Ye, W. Y. Li, L. Liu, Z. J. Fu, D. Zhu, W. Y. Li, K. Li, F. Zou, X. Ouyang, H. Xiao, Z. Ping, H. L. Zhu, *Med. Chem.* **2021**, *17*, 1046-1059.

[3] Reviews for the thiourea based organocatalysis: a) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed*. **2006**, *45*, 1520-1543; c) S. J. Connon, *Chem. Eur. J*. **2006**, *12*, 5418–5427; d) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; e) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev*. **2009**, *38*, 1187–1198; f) W. Y. Siau, J. Wang, *Catal. Sci. Technol*. **2011**, *1*, 1298–1310; g) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051–7071; h) Z. Zhang, Z. Bao, H. Xing, *Org. Biomol. Chem.* **2014**, *12*, 3151–3162; i) M. Žabka, R. Šebesta, *Molecules* **2015**, *20*, 15500–15524; j) N. Busschaert, C. Caltagirone, W. Van Rossom, P. A. Gale, *Chem. Rev*. **2015**, *115*, 8038-8155; k) X. Fang, C. J. Wang, *Chem. Commun*. **2015**, *51*, 1185–1197; l) J. E. Camp, *Eur. J. Org. Chem.* **2017**, *2017*, 425–433; m) T. Parvin, R. Yadav, L. H. Choudhury, *Org. Biomol. Chem.* **2020**, *18*, 5513–5532; n) Q. Zhao, C. Chen, J. Wen, X. Q. Dong, X. Zhang, *Acc. Chem. Res.* **2020**, *53*, 1905-1921; o) S. Gandhi, V. Sivadas, B. Baire, *Eur. J. Org. Chem.* **2021**, 220-234.

[4] a) K. N. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*, 487-487; b) F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev*. **2012**, *41*, 2406-2447; c) R. B. Sunoj, *Acc. Chem. Res*. **2016**, *49*, 1019-1028; d) S. Otocka, M. Kwiatkowska, L. Madalinska, P. Kiełbasiński, *Chem. Rev*. **2017**, *117*, 4147-4181; e) Y. B. Wang, B. Tan, *Acc. Chem. Res*. **2018**, *51*, 534-547; f) Y. C. Zhang, F. Jiang, F. Shi, *Acc. Chem. Res*. **2019**, *53*, 425-446; g) X. Y. Chen, Z. H. Gao, S. Ye, *Acc. Chem. Res*. **2020**, *53*, 690-702; h) Z. L. Li, G. C. Fang, Q. S. Gu, X. Y. Liu, *Chem. Soc. Rev*. **2020**, *49*, 32-48; i) Z. L. Xia, Q. F. Xu-Xu, C. Zheng, S. L. You, *Chem. Soc. Rev*. **2020**, *49*, 286-300. J) J. K. Cheng, S. H. Xiang, S. Li, L. Ye, B. Tan, *Chem. Rev*. **2021**, *121*, 4805-4902; k) L. Liao, X. Zhao, *Acc. Chem. Res*. **2022**, *55*, 2439-2453; l) D. Jovanovic, S. M. Huber, *Chem. Rev*. **2023**, *123*, 10527-10529.

[5] a) J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293-4296; b) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713-4716.

[6] a) X. G. Liu, J. J. Jiang, M. Shi, *Tetrahedron. Asymmetry*. **2007**, *18*, 2773-2781; b) Y.-L. Shi, M. Shi, *Adv. Synth. Catal*. **2007**, *349*, 2129-2135.

[7] a) Y. Nakayama, Y. Hidaka, K. Ito, *Synlett* **2013**, *24*, 883-885; b) P. Bobal, J. Otevrel, *Synthesis* **2016**, *49*, 593-603; c) J, Otevrel, P. Bobal, *J. Org. Chem*. **2017**, *82*, 8342-8358; d) Y. Nakayama, T. Gotanda, K. Ito, *Tetrahedron Lett*. **2011**, *52*, 6234-6237.

[8] a) J.-S. Lin, P. Yu, L. Huang, P. Zhang, B. Tan, X.-Y. Liu, *Angew. Chem. Int. Ed*. **2015**, *54*, 7847-7851; b) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc*. **2016**, *138*, 9357-9360; c) Z.-L. Yu, Y.-F. Cheng, N.-C. Jiang, J. Wang, L.-W. Fan, Y. Yuan, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, *Chem. Sci*.

2020, *11*, 5987-5993; d) R. Takagi, D.-T. Duong, *Org. Biomol. Chem*. **2021,** *19*, 8806-8811; e) J.-S. Lin, T.-T. Li, G.-Y. Jiao, Q.-S. Gu, J.-T. Cheng, L. Lv, X.-Y. Liu, *Angew. Chem. Int. Ed*. **2019**, *58*, 7092-7096.

[9] a) M. Wang, M. Feng, B. Tang, X. Jiang, *Tetrahedron Lett*. **2014**, *55*, 7147–7155; b) K. S. Petersen, *Tetrahedron Lett*. **2015**, *56*, 6523–6535; c) A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson, D. J. Dixon, *Chem. Soc. Rev*. **2016**, *45*, 5474–5540; d) Z. Wang, W.-X. Hong, J. Sun, *Curr. Org. Chem*. **2016**, *20*, 1851–1861; e) X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, J. Zhou, *Chem. Rev*. **2016**, *116*, 7330–7396; f) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, *Science*. **2018**, *359*, 4798.

[10] NHCs-catalyzed desymmetrization of dialdehydes, see: a) J. Liu, M. Zhou, R. Deng, P. Zheng, Y. R. Chi, *Nat Commun.* **2022**, *13*, 4793; b) M. Zhou, J. Liu, R. Deng, Q. Wang, S. Wu, P. Zheng, Y. R. Chi, *ACS Catal*. **2022**, *12*, 7781-7788; c) X. Lv, J. Xu, C. Sun, F. Su, Y. Cai, Z. Jin, Y. R. Chi, *ACS Catal*. **2022**, *12*, 2706-2713; d) Y.-T. Wu, M.-R. Li, J.-Q. Sun, G.-F. Zheng, Q. Zhang, *Angew. Chem. Int. Ed*. **2022**, *61*, e202117340; e) W. Xiao, L. Lu, H. Jiang, X. He, J. Liu, W. Zhao, *Chin. J. Org. Chem*. **2022**, 42, 2504; f) S. Shee, S. S. Ranganathappa, M. S. Gadhave, R. Gogoi, A. T. Biju, *Angew. Chem. Int. Ed. 2023, e202311709*; g) B.-A. Zhou, X.-N. Li, C.-L. Zhang, Z.-X. Wang, S. Ye, *Angew. Chem. Int. Ed*. **2023**, DOI: 10.1002/anie.202314228; Desymmetrization of dialdehydes for axial chirality with other catalyst, see: h) B. Yuan, A. Page, C. P. Worrall, F. Escalettes, S. C. Willies, J. J. W. McDouall, N. J. Turner, J. Clayden, *Angew. Chem. Int. Ed.* **2010**, *49*, 7010–7013; i) S. Staniland, B. Yuan, N. Gimnez-Agull, T. Marcelli, S. C. Willies, D. M. Grainger, N. J. Turner, J. Clayden, *Chem. Eur. J.* **2014**, *20*, 13084-13088; j) L.-L. Dai, Y.-H. Liu, Q. Xu, M.-F. Wang, Q.-H. Zhu, P.-Y. Yu, G.-F. Zhong, X.-F. Zeng, *Angew. Chem. Int. Ed*. **2023**, *62*, e202216534; k) F. Huang, L.-F. Tao, J.-Y. Liu, L.-H. Qian, J.-Y. Liao, *Chem. Commun*. **2023**, *59*, 4487; l) H. Jiang, X.-K. He, X. Jiang, W. Zhao, L.-Q. Lu, Y. Cheng, W.-J. Xiao, *J. Am. Chem. Soc*. **2023**, *145*, 6944–6952; m) T. Liang, Y. Wu, J. Sun, M. Li, H. Zhao, J. Zhang, G. Zheng, Q. Zhang, *Chin. J. Chem*. **2023**, *41*, 3253-3260.

[11] Selected reviews see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606-5655; b) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511-3522; c) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485-496; d) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040-5052; e) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307-9387; f) K. J. Murauski, A. A. Jaworski, K. A. Scheidt, *Chem. Soc. Rev.* **2018**, *47*, 1773-1782; g) X. Chen, Z. Gao, S. Ye, *Acc. Chem. Res.* **2020**, *53*, 690-702; h) P. Bellotti, M. Koy, M. N. Hopkinson, F. Glorius, *Nat. Rev. Chem.* **2021**, *5*, 711.

[12] Selected reviews see: a) Y. Sumida, H. Ohmiya, *Chem. Soc. Rev.* **2021**, *50*, 6320-6332; b) L. Dai and S. Ye, *Chin. Chem. Lett.* **2021**, *32*, 660-667; c) K. Liu, M. Schwenzer, A. Studer, *ACS Catal*. **2022**, *12*, 11984-11999; d) J. Sun, L. Wang, G. Zheng, Q. Zhang, *Org. Chem. Front.* **2023**, *10*, 4488-4515; e) H. Wang, F. Su, Y. Wang, X. Wu, Y. R. Chi, *Org. Chem. Front.* **2023**, *10*, 5291-5295; f) X. Wang, S. Wu, R. Yang, H. Song, Y. Liu, Q. Wang, *Chem. Sci.* **2023**, *14*, 13367-13383.

[13] a) S. Lu, S. B. Poh, Y. Zhao, *Angew. Chem. Int. Ed*. **2014**, *53*, 11041-11045; b) D. Guo, Q. Peng, B. Zhang, J. Wang, *Org. Lett.* **2021**, *23*, 7765-7770; c) S. Lu, J. Y. Ong, H. Yang, S. B. Poh, X. Liew, C. S. D. Seow, M. W. Wong, Y. Zhao, *J. Am. Chem. Soc*. **2019**, *141*, 17062−17067; d) C. Zhao, D. Guo, K. Munkerup, K. Huang, F. Li, J. Wang, *Nat. Commun*. **2018**, *9*, 611; e) K. Xu, W. Li, S. Zhu, T. Zhu, *Angew. Chem. Int. Ed*. **2019**, *58*, 17625-17630; f) C. Zhang, Y. Gao, H. Wang, B. Zhou, S. Ye, *Angew. Chem. Int. Ed*. **2021**, *60*, 13918-13922; *Angew. Chem.* **2021**, *133*, 14037–14041; g) T. Li, C. Mou, P. Qi, X. Peng, S. Jiang, G. Hao, W. Xue, S. Yang, L. Hao, Y. R. Chi, Z. Jin, *Angew. Chem. Int. Ed*. **2021**, *60*, 9362–9367; h) Y. Lv, G. Luo, Q. Liu, Z. Jin, X. Zhang, Y. Chi, *Nat. Commun*. **2022**, *13*, 36; i) B. Mondal, H. Chen, R. Maiti, H. Wang, H. Cai, C. Mou, L. Hao, H. Chai, Y. Chi, *Org. Lett*. **2023**, DOI: 10.1021/acs.orglett.3c03141; j) S. Zhang, X. Wang, L. Han, J. Li, Z. Liang, D. Wei, D. Du, *Angew. Chem. Int. Ed*. **2022**, *61*, e202212005; k) J. Yan, R. Maiti, S. Ren, W. Tian, T. Li, J. Xu, B. Mondal, Z. Jin, Y. Chi, *Nat. Commun*. **2022**, *13*, 84; l) S. Zhang, S. Liu, X. Wang, S. Wang, H. Yang, L. Li, B. Yang, M. W. Wong, Y. Zhao, S. Lu, *ACS Catal*. **2023**, *13*, 2565−2575; m) K. Balanna, S. Barik, S. Barik, S. Shee, N. Manoj, R. G. Gonnade, A. T. Biju, *ACS Catal*. **2023**, *13*, 8752–8759.

[14] a) S. Lu, S. B. Poh, Z. Rong, Y. Zhao, *Org. Lett*. **2019**, *21*, 6169-6172; b) G. Yang, D. Guo, D. Meng, J. Wang, *Nat. Commun*. **2019**, *10*, 3062; c) S. Zhuo, T. Zhu, L. Zhou, C. Mou, H. Chai, Y. Lu, L. Pan, Z. Jin, Y. Chi, *Angew. Chem. Int. Ed*. **2019**, *58*, 1784-1788; d) S. Barik, S. Shee, S. Das, R. G. Gonnade, G. Jindal, S. Mukherjee, A. T. Biju, *Angew. Chem. Int. Ed*. **2021**, *60*, 12264-12268; e) J. Jin, X. Huang, J. Xu, T. Li, X. Peng, X. Zhu, J. Zhang, Z. Jin, Y. Chi, *Org. Lett*. **2021**, *23*, 3991-3996; f) X. Yang, L. Wei, Y. Wu, L. Zhou, X. Zhang, Y. Chi, *Angew. Chem. Int. Ed*. **2023**, *62*, e202211977; g) W. Xiao, L. Lu, H. Jiang, X. He, J. Liu, W. Zhao, *Chin. J. Org. Chem.* **2022**, *42*, 2504.

[15] a) C.-G. Zhao, D.-H. Guo, K. Munkerup, K.-W. Huang, F.-Y. Li, J. Wang, *Nat. Commun*. **2018**, 9, 611; b) S. Lu, J. Y. Ong, H. Yang, S. B. Poh, X. Liew, C. S. D. Seow, M. W. Wong, Y. Zhao, *J. Am. Chem. Soc*. **2019**, *141*, 17062-17067; c) C.-L. Zhang, Y.-Y. Gao, H.-Y. Wang, B.-A. Zhou, S. Ye, *Angew. Chem. Int. Ed*. **2021**, *60*, 13918-13922; d) T. Li, C. Mou, P. Qi, X. Peng, S. Jiang, G. Hao, W. Xue,S. Yang, L. Hao, Y. Robin Chi, Z. Jin, *Angew. Chem*. **2021**, *133*, 9448-9453; e) R. Ma, X.-X. Wang, Q.-Y Zhang, L. Chen, J. Gao, J. Feng, D.-H. Wei, D. Du, *Org. Lett.* **2021**, *23*, 4267−4272; f) Y.-P. Chu, M. Wu, F. Hu, P.-P Zhou, Z.-Q Cao, X.-P Hui, *Org. Lett*. **2022**, *24*, 3884−3889; g) G.-J. Wang, J.-H. Huang, L.-X Zhang, J.-N. Han, X.-X Zhang, J. Huang, Z.-Q. Fu, W. Huang, *Sci. China Chem*. **2022**, *65*, 1953–1961; h) S.-C. Zhang, S.-P. Liu, X. Wang, S.-J. Wang, H. Yang, L. Li, B.-M. Yang, M. W. Wong, Y. Zhao, S.-C. Lu; *ACS Catal*. **2023**, *13*, 2565−2575; i) H.-Y. Wang, Z.-C. Li, C.-L. Zhang, S. Ye, *J. Org. Chem*. **2023**, *88*, 11913−11923; j) L.-X. Zhang, Q.-Q. Wu, M. Ren, H.-L Zhang, X.-X. Zhang, J.-H. Liu, Z.-Q. Fu, *Adv. Synth. Catal*. **2023**, *365*, 3467-3472.

[16] a) L. Wang, R. Ma, J. Sun, G. Zheng, Q. Zhang, *Chem. Sci*. **2022**, *13*, 3169-3175; b) L. Wang, J. Sun, J. Xia, M. Li, L. Zhang, R. Ma, G. Zheng, Q. Zhang, *Sci. China. Chem*. **2022**, *65*, 1938-1944; c) L. Wang, J. Sun, J. Xia, R. Ma, G. Zheng, Q. Zhang, *Org. Chem. Front*. **2023**, *10*, 1047-1055; d) J. Sun, L. Wang, G. Zheng, Q. Zhang, *Org. Chem. Front*. **2023**, *10*, 4488-4515.

[17] a) Q. Zhang, S.-M. Wang, J.-J. Yin, T. Xiong, Q. Zhang, *Angew. Chem. Int. Ed*. **2022**, *61*, e202202713; b) T. Qin, G.-W. Lv, H.-R. Miao, M.-H. Guan, C.-L. Xu, G. Zhang, T. Xiong, Q. Zhang, *Angew. Chem. Int. Ed*. **2022**, *61*, e202201967; c) H.-R. Miao, M.-H. Guan, T. Xiong, G. Zhang, Q. Zhang, *Angew. Chem. Int. Ed*. **2023**, *62*, e2022139; d) X.-P. Yuan, Y.-L, Zhang, Y.-F. Li, J.-J Yin, S.-M. Wang, T. Xiong, Q. Zhang, *Angew. Chem. Int. Ed*. **2023**, *62*, e202313770.

[18] a) J. Frey, A. Malekafzali, I. Delso, S. Choppin, F. Colobert, J. Wencel-Delord, *Angew. Chem. Int. Ed.* **2020**, *59*, 8844-8848; b) S. Shaaban, H. Li, F. Otte, C. Strohmann, A. P. Antonchick, H. Waldmann, *Org. Lett.* **2020**, *22*, 9199-9202; c) H. Liang, G. Zhu, X. Pu, L. Qiu, *Org. Lett.* **2021**, *23*, 9246-9250; d) L. Lin, X.-J. Zhang, X. Xu, Y. Zhao, Z. Shi, *Angew. Chem. Int. Ed.* **2023**, *62*, e202214584; e) S. Yang, T. Zheng, L. Duan, X. Xue, Z. Gu. *Angew. Chem. Int. Ed.* **2023**, *62*, e202302749.

[19] **CCDC** 2223845 (**3ah**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Data Centre via www.ccdc.cam.ac.uk/data_request/cif.