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Versatile Method for Kinetic Resolution of Protecting-Group-Free BINAMs and NOBINs through Chiral Phosphoric Acid Catalyzed Triazane Formation

Wei Liu,[a],[b] Qianwen Jiang[a],[b] and Xiaoyu Yang*[a]

Dedicated to the 100th anniversary of the School of Chemistry and Chemical Engineering, Nanjing University and the 70th anniversary of Shanghai Institute of Organic Chemistry

Abstract: A versatile kinetic resolution of protecting-group-free BINAMs and NOBINs has been realized through chiral phosphoric acid catalyzed triazane formation with azodicarboxylates. A series of mono-*N*-protected and unprotected BINAMs, diphenyl diamines and NOBIN derivatives could be kinetically resolved with excellent performances (with *s* factor up to 420). The gram-scale reactions and facile derivatizations of the chiral products demonstrate the potential of these methods in the asymmetric synthesis of chiral catalysts and ligands.

Axially chiral biaryl compounds are important motifs in some biologically active small molecules and natural products,[1] which have also been extensively utilized as chiral catalysts/ligands in asymmetric catalysis.[2] Accordingly, the development of efficient enantioselective methods for the synthesis of axially chiral biaryls has become an important task in organic chemistry,[3] and significant progress have been made in the last two decades through organocatalysis,[4] transition metal-catalyzed couplings[5] and C-H activation[6] reactions. In particular, some functionalized axially chiral biaryls have been proven as privilege scaffolds for developing chiral catalysts and ligands, such as 1,1'-bi-2-naphthol (BINOL),[2] 1,1'-binaphthyl-2,2'-diamine (BINAM)[7] and 2-amino 2'-hydroxy-1,1'-binaphthyl (NOBIN).[8] In comparison with the plentiful methods developed for enantioselective synthesis of BINOL and its derivatives,[9] asymmetric catalytic approaches for the synthesis of chiral BINAM- and NOBIN-type biaryls are relatively elusive, and resolution using chiral reagents is still the most practical method to obtain enantioenriched BINAM and NOBIN by far.[10] List[11] and Kürti[12] group reported the enantioselective synthesis of BINAMs via chiral Brønsted acid catalyzed asymmetric [3,3]-sigmatropic rearrangement of biaryl hydrazines respectively, albeit with limited scope. Recently, Tan and co-workers developed a series of elegant asymmetric catalytic methods for asymmetric synthesis of BINAMs, NOBINs and their analogues via chiral Brønsted acid and Lewis acid catalyzed asymmetric additions of 2-naphthols and 2-naphthylamines with iminoquinones,[13] azonaphthalenes[14] and nitrosonaphthalenes.[15]

The alternative strategy for asymmetric catalytic synthesis of BINAM and NOBIN derivatives is the kinetic resolution of their racemic substrates, which have also been proven fruitful. Tan and co-workers developed a highly efficient kinetic resolution of BINAM and its derivatives through asymmetric reductive aminations (Figure 1, a).[16] Maruoka and co-workers reported the kinetic resolution of NOBIN-type biaryl amino alcohols via phase-transfer-catalyzed *N*-allylations (Figure 1, b).[17] Zhao and co-workers developed kinetic resolution of NOBINs and other biaryl amino alcohols via chiral NHC-catalyzed *O*-acylations[18] and chiral Brønsted base catalyzed *N*-alkylations[19] (Figure 1, c). Despite the fact that these methods provided practical solutions for the asymmetric synthesis of enantioenriched BINAM and NOBIN derivatives respectively, these kinetic resolution methods still suffer two major limitations: 1) no versatile kinetic resolution methods have been developed both applicable for BINAMs and NOBINs; 2) one or two protecting groups are required on the substrates to ensure the reactivities and stereoselectivities, which requires extra steps for protecting group manipulations.

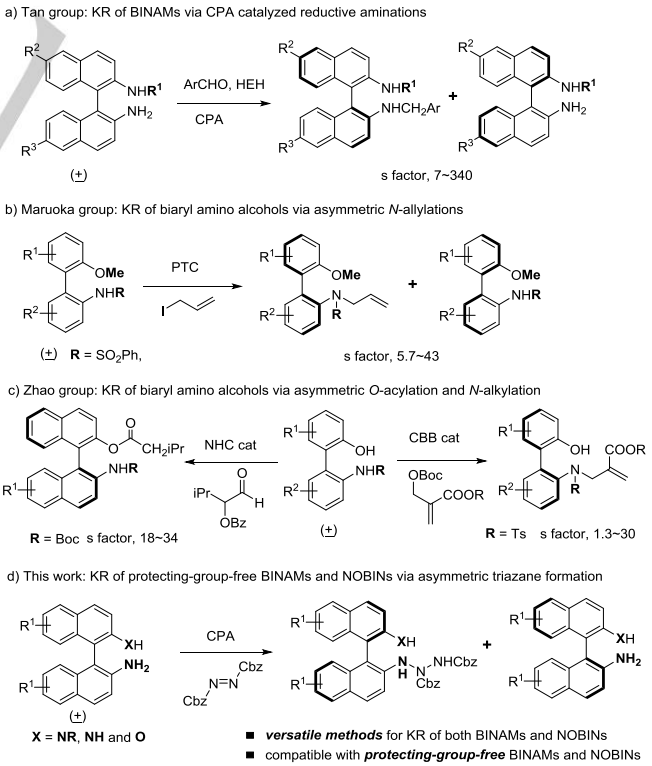

Figure 1. Asymmetric synthesis of BINAMs and NOBINs via kinetic resolution.

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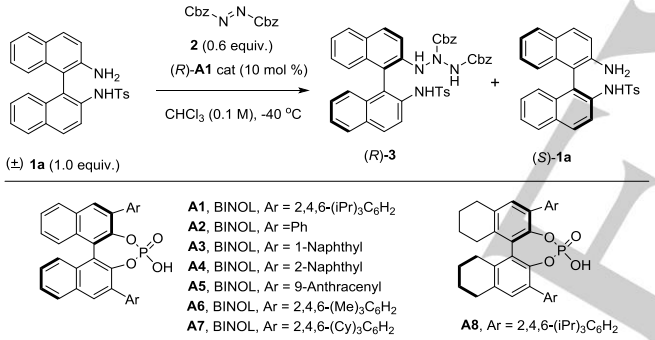
With our continuous interest on developing novel asymmetric reactions between aryl amines and azodicarboxylates,[20] herein we disclose a versatile method for kinetic resolution of protecting-group-free BINAMs and NOBINs through chiral phosphoric acid (CPA)[21] catalyzed triazane formation.

In our previous report of atroposelective construction of biaryl diamines via asymmetric *para*-amination of anilines with azodicarboxylates enabled by CPA catalysis,[20a] we observed the *N*-amination triazane[22] products were generated as the major products when the *para*-positions of anilines were blocked. Accordingly, we envisioned that if these reactions could be utilized for the kinetic resolution of axially biaryl amines, such as BINAMs and NOBINs. Thus, we initiated our study by choosing *N*-Ts protected racemic BINAM **1a** as model substrate and dibenzyl azodicarboxylate **2** as the amination reagent, under the catalysis of CPA. After careful examinations of the reaction conditions, the optimal conditions were determined, where the reaction between **1a** (1.0 equiv.) and **2** (0.6 equiv.) in the presence of TRIP (cat **A1**, 10 mol %) in $CHCl_3$ (0.1 M) at −40 °C provided the triazane product **3a** with 96% ee and the recovered (*S*)-**1a** with 92% ee, with a selectivity factor (*s*)[23] of 94 (Table 1, entry 1). The study of variation of the catalysts indicated that only the sterically bulky 2,4,6-trialkylphenyl substituted catalyst gave decent kinetic resolution performances (entry 7), while other 3,3'-disubstituted BINOL-derived CPA catalysts all provided poor results (entries 2-6). Switching the chiral scaffold of CPA catalysts from BINOL- to H8-BINOL-type also led to the erosion of s factor (entry 8). Investigation of the solvents suggested that the reaction in toluene could provide good kinetic resolution performance, however with much slower reaction rate, probably due to the poor solubility of **1a** under these conditions (entry 9); while the reactions in other solvents provided poor stereoselectivities (entries 10-11). Finally, the reaction temperature was also evaluated, which was determined to be critical for the kinetic resolution performances; the reaction at −20 °C only provided an s factor of 23 (entry 12).[24]

Table 1. Optimization of reaction conditions.

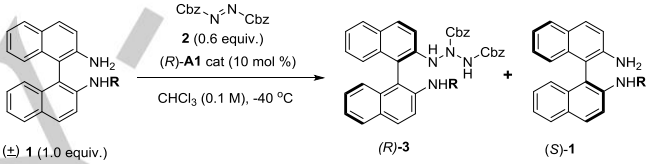


Entry[a]	Variation from the standard conditions	ee of **3** (%)[b]	ee of (*S*)-**1a** (%)[b]	C (%)[c]	*s*[d]
1	None	96	92	51	94
2	**A2** instead of **A1**	17	2.5	13	1.4
3	**A3** instead of **A1**	84	59	41	21
4	**A4** instead of **A1**	4.4	5.6	56	1.1
5	**A5** instead of **A1**	37	67	64	4.1
6	**A6** instead of **A1**	55	80	59	8.1
7	**A7** instead of **A1**	93	89	49	83
8	**A8** instead of **A1**	88	72	45	34
9	Tol instead of $CHCl_3$	98	15	13	115
10	Et_2O instead of $CHCl_3$	53	9	14	3.6
11	DCM instead of $CHCl_3$	90	91	50	60
12	−20 °C instead of −40 °C	84	67	44	23

[a]Reactions were performed with racemic **1a** (0.1 mmol), **2** (0.06 mmol) and CPA catalysts (0.01 mmol, 10 mol %) in solvents (1 mL) at designated temperature for 36 h. [b]Ee values were determined by chiral HPLC analysis. [c]Conversion (C) = $ee_s/(ee_s+ee_p)$. [d]S factor (*s*) = $\ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$.

With the optimal conditions in hand, the substrate scope for mono-*N*-protected BINAMs under the catalysis of CPA (*R*)-**A1** was firstly explored (Table 2). We were pleased to find that various common *N*-protecting groups, including Bz, Boc, Cbz and Bn, could all be well tolerated under the optimal conditions, providing both products **3** and recovered starting materials (*S*)-**1**[25] with excellent enantioselectivities (with s factors up to 354).

Table 2. Substrate scope for kinetic resolution of *N*-protected BINAMs.

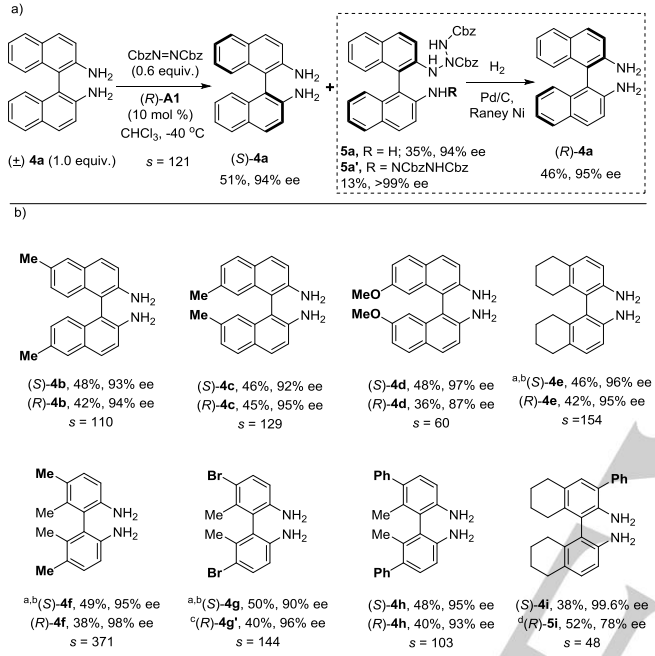


Entry[a]	Substrate	R	**3** (yield, ee)[b]	(*S*)-**1** (yield, ee)[b]	*s*[c]
1	**1a**	Ts	47%, 96% ee	48%, 92% ee	94
2	**1b**	Bz	44%, 97% ee	49%, 92% ee	101
3	**1c**	Boc	46%, 95% ee	50%, 96% ee	183
4	**1d**	Cbz	42%, 89% ee	48%, 98% ee	298
5	**1e**	Bn	48%, 94% ee	44%, 98% ee	354

[a]Reactions were performed with racemic **1** (0.2 mmol), **2** (0.12 mmol) and (*R*)-**A1** catalysts (0.02 mmol, 10 mol %) in $CHCl_3$ (2 mL) at –40 °C for 36~63 h. [b]Isolated yields. Ee values were determined by chiral HPLC analysis. [c]S factor (s) = $\ln[(1-C)(1-ee_s)]/\ln[(1-C)(1+ee_s)]$, Conversion (C) = $ee_s/(ee_s+ee_p)$.

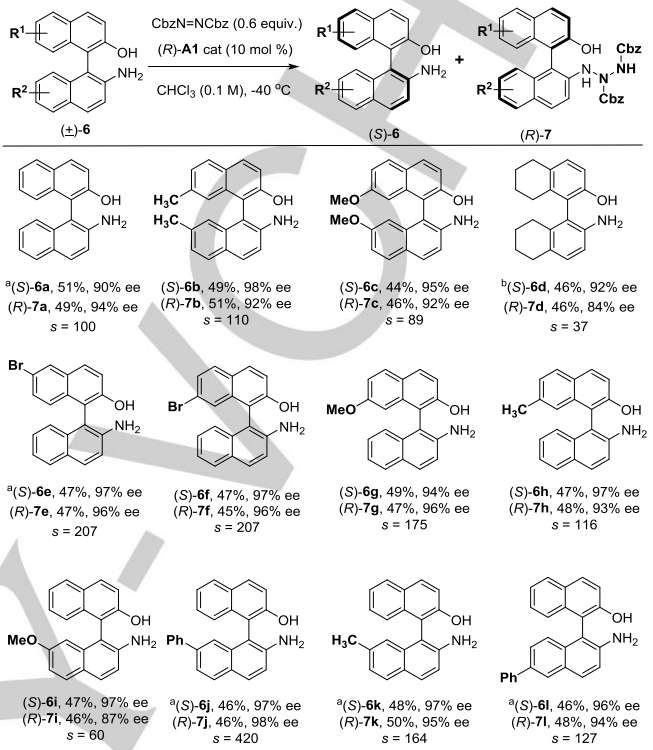
With our aim to develop a more efficient kinetic resolution protocol applicable for protecting-group-free BINAMs, the standard conditions were applied on racemic BINAM (**4a,** Scheme 1, a). Encouragingly, this reaction still provided excellent kinetic resolution performances, with the recovered (*S*)-**4a**[25] isolated in 51% yield with 94% ee and the triazane product **5a** obtained in 35% yield with 94% ee. However, the bis-triazane product **5a'** was also isolated in 13% yield in this reaction, though with excellent enantioselectivity (>99% ee). To simplify the workup procedure, after brief separation of the recovered starting material by column chromatography, the mixture products of **5a** and **5a'** were directly subjected into catalytic hydrogenation conditions, which eventually generated the other enantiomer of BINAM (*R*)-**4a** in 46% yield with 95% ee. With these satisfying results, we set out to explore the scope of this reaction (Scheme 1, b). A series of 6,6'- and 7,7'-disubstituted BINAMs could be well tolerated under the optimal conditions, providing both enantiomers of the BINAM derivatives

with high enantioselectivities (**4b**-**d**). The H8-BINAM could be well kinetically resolved under these conditions as well (**4e**), giving an s factor of 154. Additionally, the biphenyl-type diamines were also amenable substrates under the optimal kinetic resolution conditions, which gave the axially chiral biphenyl diamines with excellent enantioselectivities (**4f**-**h**). Interestingly, a 3-subsituted unsymmetrical H8-BINAM derivative was also compatible substrate, in which the triazane formation only occurred at the 1'-NH_2 group due to the steric hindrance (**5i**), while the 3,3'-disubstituted H8-BINAM could not provide any triazane product under the optimal conditions.



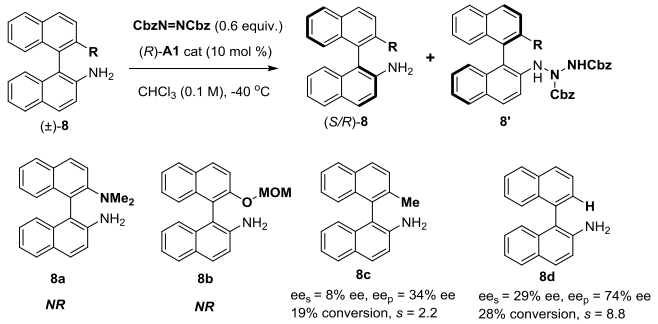
Scheme 1. Substrate scope of kinetic resolution of protecting-group-free BINAMs and biphenyl diamines. Reactions were performed with racemic **4** (0.2 mmol), **2** (0.12 or 0.14 mmol) and (*R*)-**A1** catalysts (0.02 mmol, 10 mol %) in $CHCl_3$ (2 mL) at –40 °C for 14~72 h. After completion of these reactions, the reaction mixtures were briefly separated by column chromatography to give recovered (*S*)-**4** and the mixture of **5** and **5'**, which were directly subjected to catalytic hydrogenation conditions (with Pd/C and Raney Ni as catalyst under 1 atm H_2 at 50 °C) to give the (*R*)-**4**. Isolated yields with respect of racemic **4**. Ee values were determined by chiral HPLC analysis. S factor (*s*) = ln[(1-C)(1-ee_s)]/ln[(1-C)(1+ee_s)]. [a] At -60 °C. [b] Catalytic hydrogenation was performed under 60 atm H_2 at rt. [c] Catalytic hydrogenation gave debrominated product **4g'**. [d] No catalytic hydrogenation was performed.

To demonstrate the versatility of this method, kinetic resolution of the protecting-group-free NOBIN (**6a**) was studied under the kinetic resolution conditions, which proceeded smoothly to give the recovered NOBIN (*S*)-**6a**[25] in 51% yield with 90% ee and the triazane product **7a** in 49% yield with 94% ee, with an s factor of 100 (Scheme 2, **6a**). With these encouraging results, we started to explore the scope of kinetic resolution of NOBIN derivatives. A series of 7,7'-disubstituted symmetrical NOBINs were well tolerated under the standard conditions (**6b**-**c**), including the H8-NOBIN (**6d**). Next, a range of 6- and 7-substituted NOBIN analogues were examined, which provided excellent kinetic resolution performances (**6e**-**h**). Finally, we found that a range of 6'- and 7'-substituted NOBIN derivatives were also amenable substrates under the optimal kinetic resolution conditions, affording both recovered starting material and triazane products with high enantioselectivities (**6i**-**l**), with s factors up to 420.



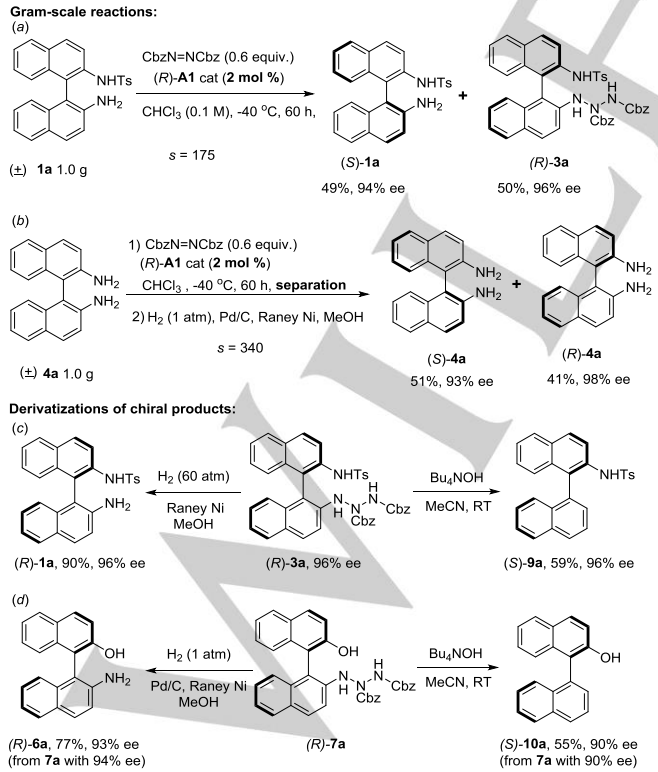
Scheme 2. Substrate scope of kinetic resolution of protecting-group-free NOBIN derivatives. Reactions were performed with racemic **6** (0.2 mmol), **2** (0.12 mmol) and (*R*)-**A1** catalysts (0.02 mmol, 10 mol %) in $CHCl_3$ (2 mL) at −40 °C for 16~96 h. Isolated yields. Ee values were determined by chiral HPLC analysis. S factor (*s*) = ln[(1-C)(1-ee_s)]/ln[(1-C)(1+ee_s)]. [a] **2** (0.4 mmol) and $CHCl_3$ (16 mL) was used instead. [b] −60 °C instead of −40 °C.

To shed light on the reaction mechanism, some control experiments were conducted (Scheme 3). Interestingly, applying the optimal kinetic conditions to *N,N*-dimethyl-substituted BINAM (**8a**) and *O*-MOM-protected NOBIN (**8b**) barely provided any triazane products under the standard conditions. Using 2'-methyl-substituted bisnaphthyl amine **8c** as substrate under the optimal conditions led to low conversion (19% conversion) and poor stereoselectivity (*s* = 2.2). Performing the optimal conditions on bisnaphthyl amine **8d** readily provided the recovered **8d** with 29% ee and triazane product with 74% ee, with an s factor of 8.8. All these results clearly indicated that the nonreactive –NHR, -NH_2 and –OH groups in the mono-protected BINAMs **1**, protecting-group-free BINAMs **4** and NOBINs **6** played a crucial role in modulating both the reactivities and stereoselectivities in these reactions, probably through the extra hydrogen-bonding interaction with the catalyst.



Scheme 3. Control experiments.

To demonstrate the practicability of these reactions, two gram-scale kinetic resolution reactions were performed. Kinetic resolution of 1 g of racemic *N*-Ts BINAM **1a** with 2 mol% of (*R*)-**A1** catalyst under the optimal conditions produced the triazane product **3a** in 50% yield with 96% ee and recovered (*S*)-**1a** in 49% yield with 94% ee (with an s factor of 175, Scheme 4, a). Analogously, applying the two-step procedure with 2 mol% of (*R*)-**A1** catalyst on racemic BINAM (**4a**, 1.0 g) afforded the (*S*)-**4a** in 51% yield with 93% ee and (*R*)-**4a** in 41% yield with 98% ee (with an s factor of 340, Scheme 4, b). The derivatizations of the chiral products were also investigated to prove the applicability of these reactions. The facile hydrogenation of the triazane products **3a** and **7a** generated the *N*-Ts BINAM (*R*)-**1a** and NOBIN (*R*)-**6a** in high yields, without erosion of the ee values. Interestingly, we found that treatment of triazane products with Bu_4NOH[26] would give the deamination products in moderate yields. Accordingly, the 2-amino-1,1'-binaphthyl (*S*)-**9a** and 1,1'-binaphthalen]-2-ol (*S*)-**10a** were readily prepared from the triazane products **3a** and **7a**, with retained optical purities (Scheme 4, c and d).



Scheme 4. Gram-scale reactions and derivatizations of chiral products.

In conclusion, we have developed the first versatile kinetic resolution of protecting-group-free BINAMs and NOBINs through triazane formation with azodicarboxylates enabled by chiral phosphoric acid catalysis. These reactions featured highly broad substrate scopes, in which various *N*-protected BINAMs, protecting-group-free BINAM derivatives, biphenyl diamines and NOBIN analogous could be kinetically resolved with excellent performances (with s factors up to 420). The easy scale-up of these reactions with reduced catalyst loading and facile derivatizations of the chiral products well demonstrate the applicability of these methods, especially in the field of asymmetric synthesis of chiral ligands and catalysts. Further application of these reactions in kinetic resolution of arylamines and utility of the triazane functional group are under investigation in our lab.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: kinetic resolution• organocatalysis • BINAMs • NOBINs • protecting-group-free

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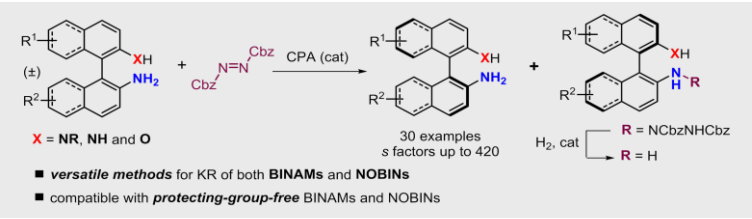

A highly efficient and versatile method for kinetic resolution of protecting-group-free BINAMs and NOBINs has been developed through chiral phosphoric acid catalyzed triazane formation with azodicarboxylates. The broad substrate scope and excellent kinetic performances of these methods and facile transformations of the triazane products demonstrate the value of these methods in preparation of axially chiral biaryl diamines and amino alcohols.

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