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DIASTEREOSELECTIVE SYNTHESIS OF AMIDE-BRIDGED AXIALLY CHIRAL BIARYLS THROUGH POINT-TO-AXIAL ASYMMETRIC C-H ARYLATION

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Abstract – Amide-bridged axially chiral biaryls are important structural motif in natural products and pharmaceuticals. Herein we report a highly efficient C-H activation method to afford a novel kind of modifiable amide-bridged axially chiral biaryls. This approach has a broad scope, enabling the synthesis of various axially chiral biaryls with good reactivity and excellent diastereoselectivity. The axially chiral biaryl could be easily transformed to a new amide-bridged atropisomeric monophosphine ligand, which represent the high potential in asymmetric synthesis and catalysis.

Axially chiral biaryls are intriguing molecular scaffolds present in a broad range of biologically active natural products,[1] pharmaceutical drugs (steganacin, korupensamin, vancomycin, etc.)[2] and advanced materials.[3] Moreover, they serve as efficient ligands or essential intermediates in asymmetric synthesis.[4] Consequently, great efforts have been made to obtain numerous axially chiral biaryls with novel structures through different synthetic routes.[5] The employment of a heterocyclic rings as the bridge of biaryl system could hinder the rotation, thus avoid the necessary using of bulky *ortho* substituents to maintain configurational stability.[5] However, compared with the widely studied BINAP, MOP, BINOLs and their derivatives, only a small amount of hetero-bridged axially chiral biaryls have been reported, most of which have to employ expensive chiral diols or their derivatives as the hetero-bridge during synthesis.[6] The amide-bridged axially chiral biaryls are structural motifs existed in biologically active natural products and pharmaceuticals, as well as in a few ligands.[7] Assembling the easily modifiable amide group into axially chiral biaryls could therefore stimulate the development of novel pharmaceuticals and ligands through potential derivatization of a wide variety of systematically designed analogues. Despite the aforementioned attractive features, efficient synthetical strategy to access such atroisomeric moieties are still scarce.[7,8]

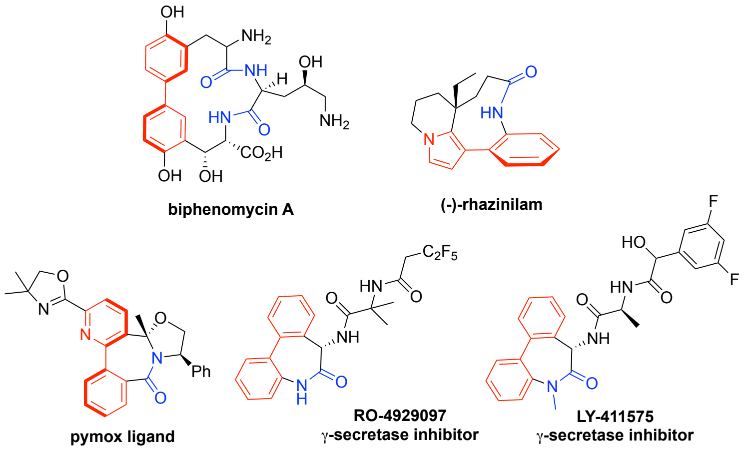


Figure 1. Importance of amide-bridged axially chiral biaryls

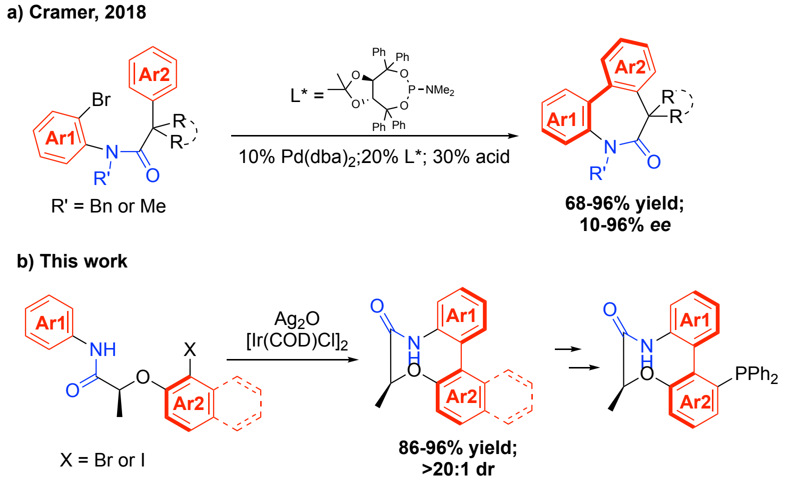
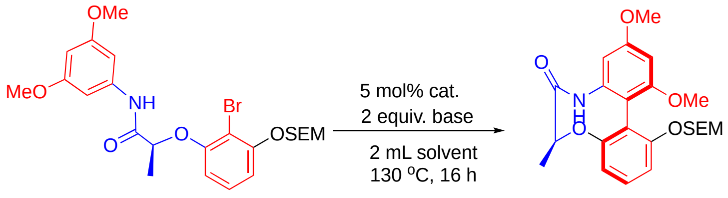


Figure 2. Synthetic strategies of amide-bridged axially chiral biaryls

Recently, the transition metal-catalyzed asymmetric C-H activation has attracted considerable attention as one of the most efficient and straightforward protocols toward diverse axially chiral biaryl cores from simple precursors.[9] However, most of the C-H activations proceed through directed functionalization *ortho* to already existed biaryl axises rather than asymmetric C-H coupling of two aryl counterparts. The later strategy suffered from limited substrate scope and unsatisfying enantiopurity, thus remain a barely explored field. In 2018, Cramer *et al.*[10] reported the first synthetic strategy to lactam-bridged axially chiral biaryls trough atropo-enantioselective C-H coupling of two aryl counterparts, affording dibenzazepinones with medium yields and 68-96% ee (Figure 2. a). Whilst the substituent group on the nitrogen atom of the lactam bridge has to be methyl or benzyl, or the enantioselectivity would decrease to 10%. Therefore it is difficult to obtain other lactam-bridged axial chiral biaryl analogues through this methodology, which is detrimental to its application. To address this synthetic challenge, we planned to design a general, step-economic and stereoselective protocol focusing on point-to-axial C-H arylation (Figure 2. b).

However, this protocol might suffer from low chemoselectivity when Ar1 comprises a *meta* substituent. In addition, the typically elevated reaction temperature might cause a large amount of dehalogenated byproducts as well as facilitate the racemization, thus reduce the stereoselectivity. To our delight, this atroposelective route proved to be of excellent reactivity and stereoselectivity. A broad range of amide-bridged axially chiral biaryls were synthesized with high optical purity and could be easily transferred to a new kind of ligand.

Table 1. Optimization of the reaction conditions[a]



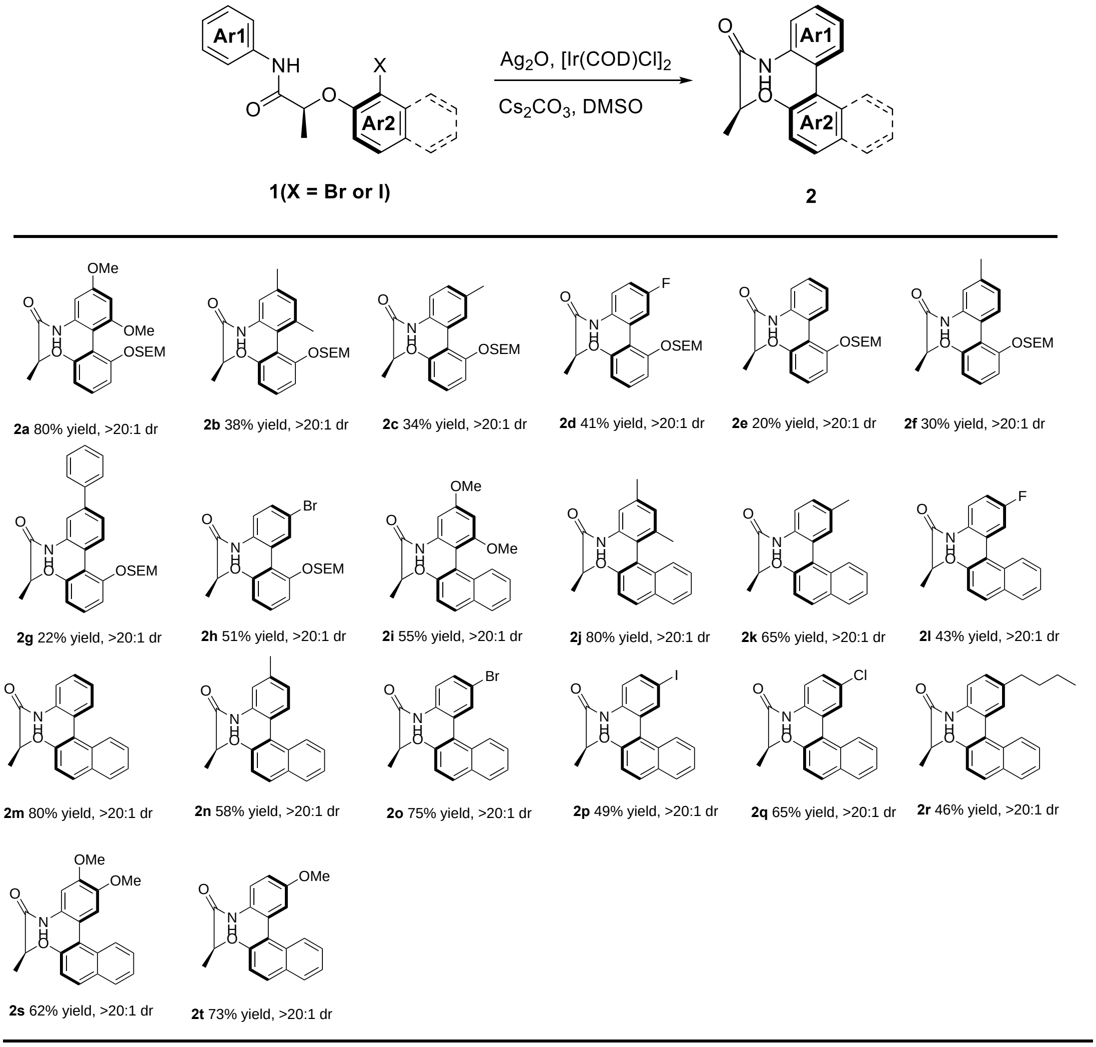
***S*-1a** **(*S*,*S*$_a$)-2a**

Entry	Conditions	Conv. (%)[b]	Yield (%)[c]	dr of **2a** (%)[d]
1	$Pd(OAc)_2$, Ag_2O, Cs_2CO_3, DMSO	50	45	>20:1
2	$Pd(CF_3COO)_2$, Ag_2O, Cs_2CO_3, DMSO	45	40	>20:1
3	$PdCl_2$dppf, Ag_2O, Cs_2CO_3, DMSO	50	50	>20:1
4	$[Ir(COD)Cl]_2$, Ag_2O, Cs_2CO_3, DMSO	80	80	>20:1
5	$[Rh(Cp^*)Cl_2]_2$, Ag_2O, Cs_2CO_3, DMSO	70	60	>20:1
6	$[Ir(COD)Cl]_2$, Ag_2O, K_2CO_3, DMSO	60	60	>20:1
7	$[Ir(COD)Cl]_2$, Ag_2O, K_3PO_4, DMSO	55	55	>20:1
8	$[Ir(COD)Cl]_2$, Ag_2O, NaOH, DMSO	75	75	>20:1
9	$[Ir(COD)Cl]_2$, Ag_2O, Na_2CO_3, DMSO	65	65	>20:1
10	$[Ir(COD)Cl]_2$, Ag_2O, Cs_2CO_3, toluene	10	10	>20:1
11	$[Ir(COD)Cl]_2$, Ag_2O, Cs_2CO_3, 1,4-dioxane	100	40	>20:1
12	$[Ir(COD)Cl]_2$, Ag_2O, Cs_2CO_3, DMF	70	70	>20:1
13	$[Ir(COD)Cl]_2$, Ag_2O, Cs_2CO_3, DMA	78	78	>20:1

[a] Reaction conditions: ***S*-1a** (0.1 mmol) in 2 mL solvent, M catalyst (5.0 mol%), Ag_2O (0.2 mol), base (2.0 equiv.), stirred at 130 °C for 16 h. [b] Determined by ^{1}H NMR analysis of the crude product with 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by ^{1}H NMR analysis of the crude product

As an initial examination on the stereoselective C-H arylation, **1a** bearing a stereogenic lactamide group was chosen as the model substrate. Several palladium complexes proven to be efficient catalysts for C-H activation were examined with Cs_2CO_3 as the additive and toluene as the solvent. As shown in Table 1, different transition metals have good yield for reaction (Table 1, entries 1-5), especially $[Ir(COD)Cl]_2$, which can reach 80% yield. Subsequently, several additives were investigated but all of them failed to gain higher reactivity or stereoselectivity than Cs_2CO_3 (Table 1, entry 4 vs entries 6-9). More importantly, different solvents such as 1,4-dioxane, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) were also screened, dimethyl sulfoxide (DMSO) turned out to be optimal in terms of both reactivity and stereoselectivity, affording **2a** with 80% yield and >20:1 dr value (Table 1, entry 4 vs entries 10-13).

Scheme 1. Synthesis of axially chiral biaryls[a]



1(X = Br or I)

2

2a 80% yield, >20:1 dr

2b 38% yield, >20:1 dr

2c 34% yield, >20:1 dr

2d 41% yield, >20:1 dr

2e 20% yield, >20:1 dr

2f 30% yield, >20:1 dr

2g 22% yield, >20:1 dr

2h 51% yield, >20:1 dr

2i 55% yield, >20:1 dr

2j 80% yield, >20:1 dr

2k 65% yield, >20:1 dr

2l 43% yield, >20:1 dr

2m 80% yield, >20:1 dr

2n 58% yield, >20:1 dr

2o 75% yield, >20:1 dr

2p 49% yield, >20:1 dr

2q 65% yield, >20:1 dr

2r 46% yield, >20:1 dr

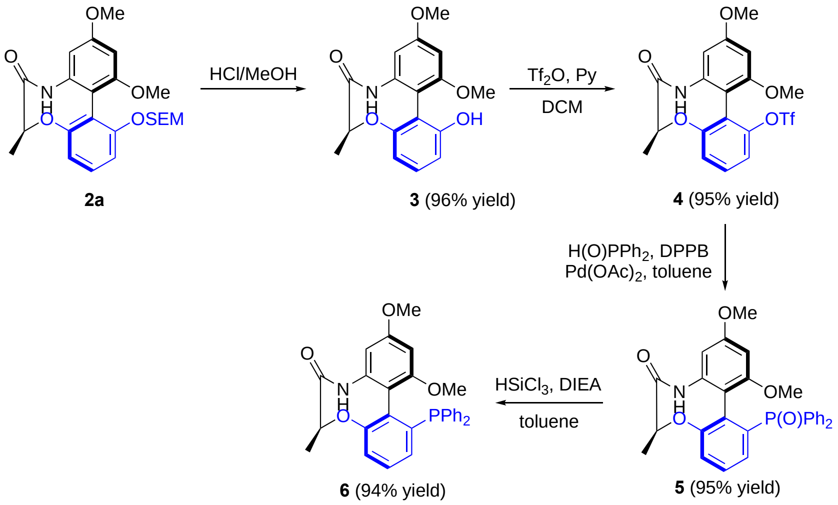
2s 62% yield, >20:1 dr

2t 73% yield, >20:1 dr

[a] Reaction conditions: ***S*-1** (0.1 mmol) in 2 mL solvent, $[Ir(COD)Cl]_2$ (5.0 mol%), Ag_2O (0.2 mol), Cs_2CO_3 (2.0 equiv.), stirred at 130 °C for 16 h; dr values are determined by ^1H NMR analysis of the crude product and yields are combined isolated values; SEM is short for 2-(trimethylsilyl)ethoxymethyl

Under the optimized reaction conditions, a variety of substrates with different substituents or scaffolds were subjected to the C-H arylation reaction, affording the desired amide-bridged axial chiral biaryl **2a-t** in excellent yields and stereoselectivities. As shown in Scheme 1, the introduction of electron-donating or electron-withdrawing substituents at the *para*-position of the amide group gave good yields and stereoselectivities (**2c**, **2d**, **2h**, **2k**, **2l** and **2o-2t**). Meantime, the substrates bearing linear alkyl chains at the *para*-position of the amide groups can also proceed smoothly in good yields (**2r**). The reaction conditions for this C-H arylation protocol work well even for sterically hindered substrates with one or two substituents *meta*-position to amide groups, proceeding smoothly to deliver the desired atropopure scaffolds (**2b**, **2f**, **2g**, **2i**, **2j**, **2n** and **2s**). Interestingly, when assembling 2-(trimethylsilyl)ethoxymethoxy (OSEM) substituent, an excellent protecting and leaving group used in certain organic reactions, into the *para*-position of different biphenyl axials, atropopure products were obtained (**2a-2h**).

Having established the efficient route to the construction of a series of atropopure amide-bridged axially chiral biaryls, to further demonstrate the synthetic utility of this protocol, we explored the further derivatization of the axial chiral biaryl product. Through four conventional steps used in the synthesis of monophosphine ligand, a novel amide-bridged atropisomeric monophosphine ligand were synthesized with a total yield of 70% and sustained atropopurity (Scheme 2).



Scheme 2. Synthesis of axially chiral biaryl monophosphine ligand **6**

In conclusion, we have demonstrated a highly atroposelective and efficient C-H arylation. A broad range of atropopure amide-bridged axiall chiral biaryls were obtained in good yields. This new protocol thus provides a practical approach for the construction of optically pure amide-bridged axially chiral biaryls and novel ligands based on the similar scaffold. We believe that this strategy will stimulate future work on the development of other challenging axially chiral biaryls and noval ligands.

ACKNOWLEDGEMENTS

Acknowledgements may be included as a separate section.

SUPPORTING INFORMATION

The supporting information includes experimental information and ^{1}H and ^{13}C NMR data for all new compounds. The data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27613/104/6

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