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Catalytic Atropenantioselective Heteroannulation between Isocyanoacetates and Alkynyl Ketones: Synthesis of Enantioenriched Axially Chiral 3-Arylpyrroles

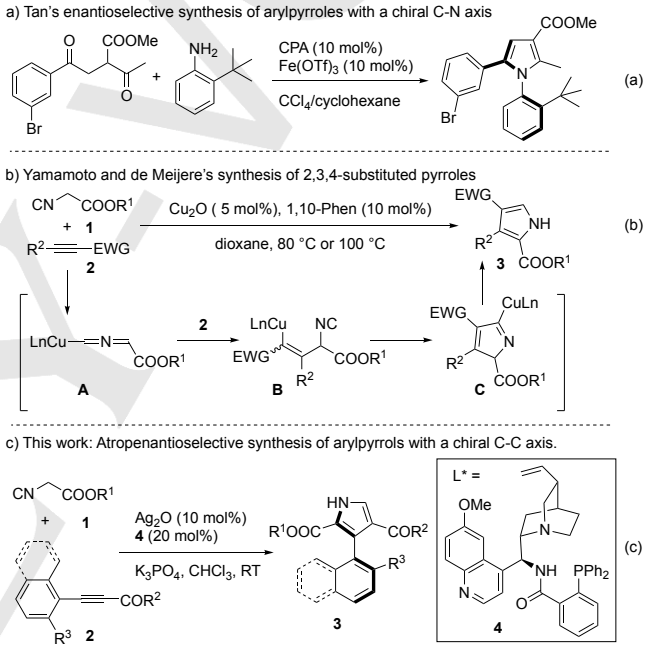
Sheng-Cai Zheng, Qian Wang, and Jieping Zhu*

Abstract: We report herein the first examples of catalytic enantioselective synthesis of axially chiral 3-arylpyrroles. Reaction of α-isocyanoacetates with β-aryl-α,β-alkynic ketones in the presence of silver oxide and a phosphine ligand derived from *Cinchona* alkaloid occurred chemoselectively to afford enantioenriched 3-arylpyrroles in high yields with excellent enantiomeric excesses. The pyrrole ring was *de novo* constructed in this process.

The axially chiral biaryl motif is found in many important natural products[1] and drugs,[2] and is a privileged structure in ligand and catalyst design.[3] Not surprisingly, the development of catalytic enantioselective synthesis of chiral biaryls has attracted attention of chemists for many years.[4] While significant progress has been recorded recently on the asymmetric synthesis of axial chiral six-membered aryl-aryl or aryl-heteroaryl compounds,[5,6] catalytic enantioselective synthesis of atropisomers bearing a five-membered heterocycles remained scarce.[7]

Pyrrole is one of the most prominent five membered heterocycles which is found in bioactive natural products and pharmaceuticals.[8] Many synthetic methodologies have been developed over a century for the synthesis of diversely substituted pyrroles.[9] Very recently, Tan and coworkers developed an elegant $Fe(OTf)_3$/chiral phosphoric acid-catalyzed enantioselective Paal-Knorr reaction for the synthesis of enantioenriched *N*-aryl substituted pyrroles bearing a chiral C-N axis (Scheme 1a).[7d]

In 2005, Yamamoto[10] and de Meijere[11] reported independently a metal catalyzed heteroannulation of isocyanoacetates **1** with activated alkynoates **2** for the synthesis of 2,3,4-trisubstituted pyrroles **3** (EWG = COOR, CN, Scheme 1b). This chemistry has subsequently been extended to terminal alkynes[12] and α-substituted α-isocyanoacetates.[13] Mechanistically, it was proposed that the reaction was initiated by the Michael addition of metallated species **A** to the alkynoate **2** to afford **B** which, upon cyclization, provided intermediate **C**. The protodemetallation and 1,5-H shift of **C** would then furnish the polysubstituted pyrrole **3**. We hypothesized that If R^2 was an aryl bearing *ortho*-substituents that could hinder the free rotation of the newly formed aryl-pyrrole bond, the resulting C3 aryl substituted pyrrole would be axially chiral. In connection with our interest in the isocyanide chemistry,[14] we became interested in developing a catalytic enantioselective version of Yamamoto-de Meijere pyrrole synthesis. We report herein that the reaction of **1** and alkynyl ketones **2** (EWG = COR^2) in the presence of Ag_2O and a Dixon-type amino phosphine ligand **4**[15] is highly atropenantioselective to afford axially chiral 3-arylpyrroles **3** in good yields with excellent enantiomeric excesses (Scheme 1c).



Scheme 1. Atropenantioselective synthesis of arylpyrroles. CPA = chiral phosphoric acid

Catalytic enantioselective addition of isocyanoacetate **1** to carbonyls,[15-16] imines,[17] electron-deficient alkenes[18] and allenes[19] are well documented in the literature. It is therefore interesting to note that enantioselective addition of isocyanoacetate **1** to alkynoates which constitutes the key step in our planned asymmetric synthesis of 3-arylpyrroles remains unknown at the outset of this work. Using Dixon's conditions developed for the aldol reaction of isocyanoacetate **1**,[15] we began our studies by examining the reaction between ethyl α-isocyanoacetate **1a** and ethyl 3-(2-methoxynaphthyl-1-yl)propiolate **5a** (Scheme 2). Performing the reaction of **1a** and **5a** at room temperature in the presence of Ag_2O (10 mol%) and the chiral phosphine **4** (20 mol%), the reaction went indeed cleanly to afford the desired arylpyrrole **6a**, albeit in moderate conversion (< 20%) and low enantioselectivity. Using phenyl ester **5b** as reaction partner, oxazole **7b**, resulting from the Claisen condensation between **1a** and **5b** followed by cyclization, was isolated as the only product. These results suggested that the

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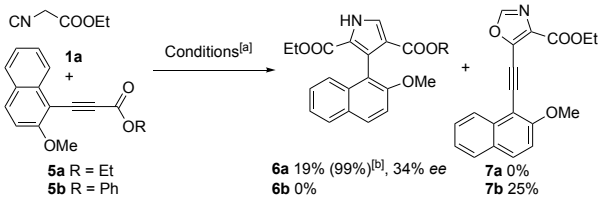
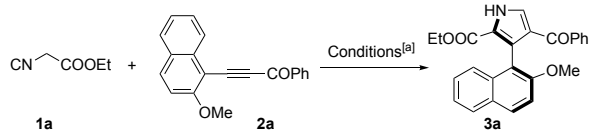
chemoselectivity of the addition reaction (1,4- *vs* 1,2-addition) is very sensitive to the subtle electronic effect of the conjugated carbonyl unit. While the results were disappointing at the first glance, the fact that **6a** was formed even at room temperature encouraged us to pursue this study.



Scheme 2. Reaction of α-isocyanoacetate with β-naphthyl substituted propiolate. [a] Ag_2O (10 mol%), **4** (20 mol%), K_3PO_4 (2.0 equiv), $CHCl_3$, RT; [b] yield based on the conversion.

Table 1. Conditions for enantioselective heteroannulation of **1a** with **2a**



Entry	Solvent	Additive	T (°C)	**3a** yield[b]	*ee*[c]
1	$CHCl_3$	-	RT	67	65
2	DCM	-	RT	57	63
3	Toluene	-	RT	45	79
4	EtOAc	-	RT	46	77
5	THF	-	RT	46	80
6	Dioxane	-	RT	35	79
7	Et_2O	-	RT	37	85
8	TBME	-	RT	42	87
9[d]	THF	-	RT	55	78
10[d]	THF	4Å MS	RT	76	80
11[d]	THF	4Å MS	0	64	87
12[d]	TBME	4Å MS	0	14	91
13[d]	THF/TBME(1:1)	4Å MS	0	53	89
14[d]	THF/TBME (1:4)	4Å MS	0	45	92
15[d]	THF/TBME (1:4)	3Å MS	0	50	90
16[d]	THF/TBME (1:4)	5Å MS	0	52	91

[a] General conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), Ag_2O (10 mol%), ligand **4** (20 mol%), solvent (*c* 0,1 M), RT, 24 h (or 0 °C, 48 h). [b] Isolated yield. [c] Determined by SFC analysis on a chiral stationary phase. [d] K_3PO_4 (2.0 equiv) was added. Abbreviation: TBME = *tert*-Butyl methyl ether.

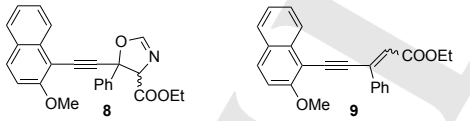
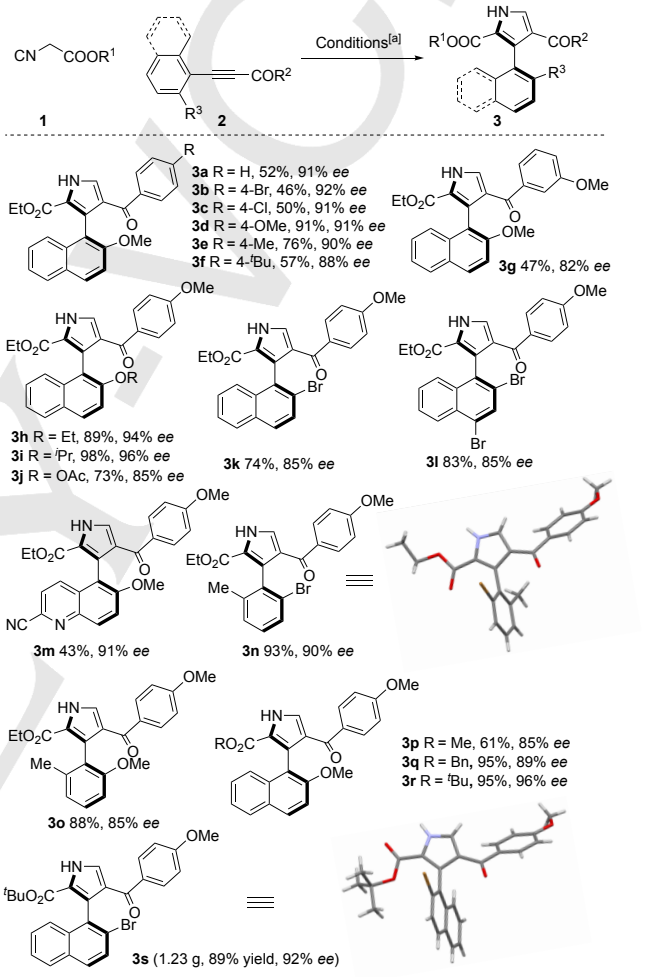


Figure 1. Side products isolated from the heteroannulation of **1a** with **2a**.

We next set out to examine the reaction of **1a** with α,β-alkynic ketone **2a** (R^3 = OMe, R^2 = Ph) in spite of the potential chemoselectivity issue (1,2- *vs* 1,4-addition). To our delight, the reaction between **1a** and **2a** in chloroform in the presence of Ag_2O (10 mol%) and the phosphine **4** (20 mol%) proceeded smoothly to afford the axially chiral 3-arylpyrrole **3a** (67% yield, 65% *ee*, entry 1, Table 1) together with two side products **8** and **9** (Figure 1) resulting from the aldol reaction. [15] The solvent has a dramatic effect on the outcome of the reaction (entries 1-8) and the higher enantioselectivity was observed in etheric solvents (entries 5-8).

Adding K_3PO_4 accelerated the reaction without having significant impact on the enantioselectivity (entry 5 *vs* 9, Table 1). After further survey of reaction conditions varying the additives, the solvents, and the reaction temperature (for details, see SI), the optimum conditions found consisted of performing the reaction of **1a** (0.12 mmol) and **2a** (0.10 mmol) in a mixed solvent (THF/TBME = 1:4, *c* 0.1 M) in the presence of Ag_2O (10 mol%), ligand **4** (20 mol%), K_3PO_4 (2.0 equiv) and 5Å MS (100 mg) at 0 °C for 48 hours. Under these conditions, 3-naphthylpyrrole (**3a**) was isolated in 52% yield with 91% *ee* (entry 16).



Scheme 3. [a] General conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), Ag_2O (10 mol%), ligand **4** (20 mol%), K_3PO_4 (2.0 equiv), THF/TBME = 1:4 (*c* 0,1 M), 5Å MS (100 mg), 48 h. Yields refer to Isolated pure compounds. The *ee* was determined by SFC analysis on a chiral stationary phase.

The substrate scope was next examined (Scheme 3). For the carbonyl part of the α,β-alkynic ketones **2**, the presence of both electron-donating and -withdrawing groups on the phenyl ring were well tolerated furnishing the products in excellent *ee*s. With an electron rich aromatic ring, the yield of the 3-arylpyrroles was excellent (e.g. **3d**, **3h**, **3i**). The acetate group was tolerated to afford **3j** and the presence of a bromide was also compatible providing compounds **3k** and **3l** with a handle for the post-functionalization. The alkynic ketone containing a quinoline system participated in the reaction to furnish **3m** in moderate yield with an excellent *ee*. Axially chiral 3-phenylpyrroles **3n** and **3o**

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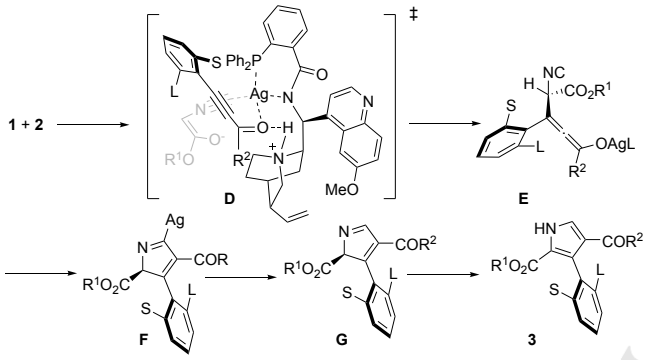
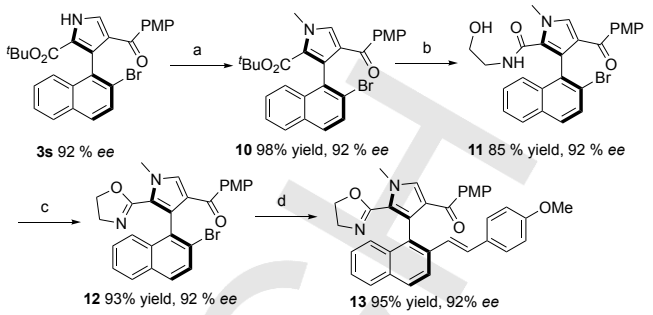
were similarly prepared in high yields and *ee*s. Different alkyl α-isocyanoacetates were examined and best results were obtained with bulky *tert*-butyl group (**3r**, 95% yield, 96% *ee*). Finally, a gram scale experiment was carried out to evaluate the practicality of the protocol. The reaction between *tert*-butyl α-isocyanoacetate **1d** and **2k** under standard conditions provided **3s** (1.23 g) in 89% yield with 92% *ee*. The absolute configuration of **3n** and **3s** was determined to be (*aR*) by X-ray diffraction analysis[20] and that of the other products were assigned by analogy. Finally, using quinidine-derived phosphine ligand, a pseudoenantiomer of **4**, (*aS*)-**3d** was obtained in 81% yield with a slightly reduced *ee* (80%, see SI). The enantiomerization barrier of **3d** was determined to be 123.7 KJ/mol at 70 °C corresponding to a half-life of 4.8 days at this temperature (See SI).



Scheme 4. Atropenantioselective process: A possible stereochemical course.

A stereochemical model implicating a (*Z*)-enolate of α-isocyanoacetate was proposed (Scheme 4).[15-18] The coordination of amide nitrogen, phosphorous, carbonyl oxygen and the divalent isocyanide carbon atoms to silver anion would define the positioning of the two reactants. The additional hydrogen bond between the protonated quinuclidine and ketone oxygen could further refine the stereochemical environment of the transition structure **D**. To minimize the steric interactions, the alkyne unit would approach the enolate from the backside to afford enantioselectively the intermediate **E**. Intramolecular addition of silver allenolate to the isocyano carbon would afford **F** which, upon protonation, provided **G**. 1,5-H shift afforded then the axially chiral 3-arylpyrroles **3** as the major enantiomer. It is worth noting that the reaction is highly chemoselective when R^2 is an electron-rich aromatic ring as the oxazoline resulting from the 1,2-additon of enolate to ketone was not observed.

Chiral arylpyrrole **3s** could be a useful starting material for the elaboration of chiral ligands/organocatalysts as illustrated in Scheme 5. The *N*-methylation of **3s** (K_2CO_3, MeI) afforded **10** which was converted to amide **11** by a sequence of hydrolysis and amidation of the resulting carboxylic acid with 2-aminoethan-1-ol. *O*-Mesylation of the primary alcohol in **11** followed by base-promoted cyclization transformed **11** to **12** without event. The Heck reaction of **12** with 1-methoxy-4-vinylbenzene afforded alkene **13** in excellent yield. No erosion of enantiomeric purity was detected in all these transformations. The olefin-oxazole ligands have been demonstrated to be useful ligands in catalytic asymmetric synthesis. [21]



Scheme 5. Transformations of **3s**. [a] MeI, K_2CO_3, DMF, RT, 98%, 92% *ee*; [b] DCM/TFA = 4:1, 0 °C, RT, then 2-aminoethan-1-ol, EDCI, HOBt, Et_3N, DCM, RT, 85%, 92% *ee*; [c] $MeSO_2Cl$, Et_3N, DCM, 0 °C, then NaOH, MeOH, 93%, 92% *ee*; [d] $Pd(OTf)_2$ (10 mol%), Bu_4NOAc (4.0 equiv), dioxane, 70-75 °C, 95%, 92% *ee*. Abbreviation: PMP = *p*-methoxyphenyl.

In summary, we developed an efficient Ag/chiral ligand-catalyzed asymmetric heteroannulation of α-isocyanoacetates with α-aryl-α,β-alkynic ketones providing 3-arylpyrroles in good to high yields with excellent enantioselectivities. The reaction displayed high chemoselectivity since alkynyl substituted oxazoline resulting from 1,2-addition of **1** to **2** was minimized under optimized conditions. To the best of knowledge, this represented the first examples of enantioselective synthesis of 3-arylpyrroles bearing a chiral C-C axis.

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Conflict of Interest

The authors declare no conflict of interest

Keywords: asymmetry synthesis • axial chirality • homogenous catalysis • isocyanide • arylpyrrole

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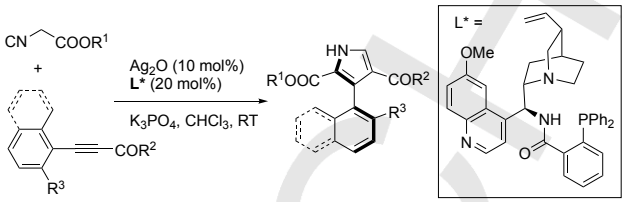
Entry for the Table of Contents (Please choose one layout)

Layout 1:

Asymmetric Synthesis

*Sheng-Cai Zheng, Qian Wang, and Jieping Zhu**_____ ***Page – Page***

Catalytic Atropenantioselective Heteroannulation between Isocyanoacetates and Alkynyl Ketones: Synthesis of Enantioenriched Axially Chiral 3-Arylpyrroles



de novo construction of pyrrole: *In the presence of a catalytic amount of Ag_2O and chiral phosphine ligand, the heteroannulation between isocyanoacetates and alkynyl ketones afforded the axially chiral 3- arylpyrroles in good yields with excellent enantioselectivities.*