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Enantioselective Synthesis of N-N Atropisomers by Palladium-Catalyzed C−H Functionalization of Pyrroles

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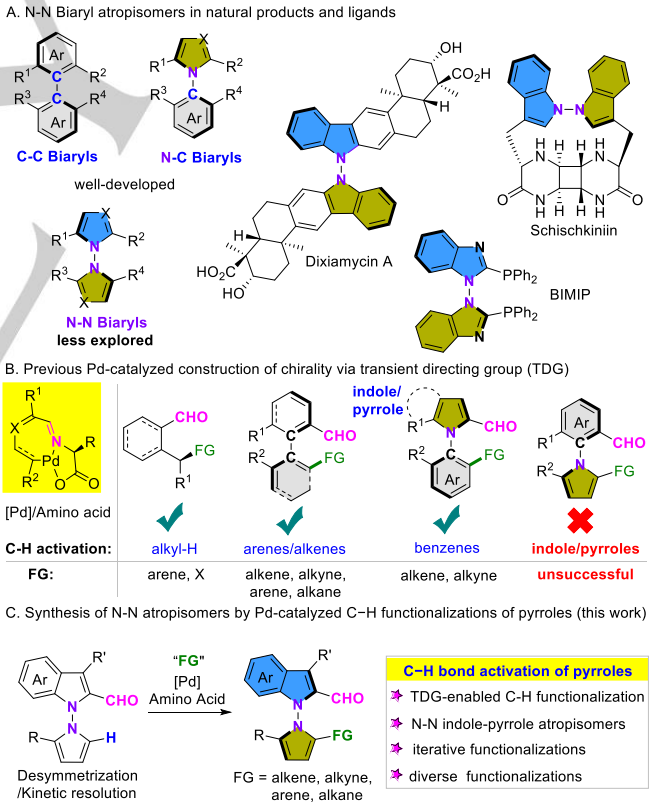
Abstract: *The catalytic asymmetric construction of N-N atropisomeric biaryls remains a formidable challenge. Studies of them lag far behind studies of the more classical carbon-carbon biaryl atropisomers, hampering meaningful development. Herein, the first palladium-catalyzed enantioselective C−H activation of pyrroles for the synthesis of N-N atropisomers is presented. Structurally diverse indole-pyrrole atropisomers possessing a chiral N-N axis were produced with good yields and high enantioselectivities by alkenylation, alkynylation, allylation, or arylation reactions. Furthermore, the kinetic resolution of trisubstituted N-N heterobiaryls with more sterically demanding substituents was also achieved. Importantly, this versatile C-H functionalization strategy enables iterative functionalization of pyrroles with exquisite selectivity, expediting the formation of valuable, complex, N-N atropisomers.*

Introduction

Atropisomers with conformationally restrained stereogenic axes are important chemical frameworks that represent the core structure of many natural products, pharmaceutically active compounds, or agrochemicals.[1] In the last decades, a variety of atropisomeric frameworks, including biphenyls, aryl amides, anilides and lactams, bearing a C−C[2] or C−N axis[3] have been constructed via the atroposelective synthesis.

The possibility of nitrogen-nitrogen atropisomerism was first considered in the 1930s but the topic was under-investigated in the decades following.[4] In recent years, however, intriguing natural products, bioactive molecules, and ligands that exhibit N–N atropisomerism have been found (Scheme 1A).[5-7] For instance, nitrogen-nitrogen indole atropisomerism is observed in the indolo-sesquiterpene natural products dixiamycin A and B, both of which show antibacterial activity.[5] Bisindole atropisomerism is also found in compounds such as schischkiniin, which is isolated from the seeds of the thistle Centaurea schischkini.[6] Moreover, N–N bibenzimidazole was found to be a framework in the biphosphine ligand BIMIP.[7] In light of the widespread occurrence of N–N atropisomerism and its importance in pharmaceutical studies, strategies for the synthesis of these compounds are of particular interest. However, the effective enantioselective synthesis of N−N atropisomers has remained elusive until recently.[8] Since 2021, a limited number of strategies for the atropoelective construction of N-N atropisomers have been developed by us and other groups via organocatalytic N–H functionalization,[9] Lewis acid catalytic desymmetrization[10] or *de novo* construction of pyrroles/indoles.[11] However, research into the synthesis of optically active N-N atropisomers is still in its early stages and, therefore, developing strategies to achieve this synthesis is a topic of great importance.



Scheme 1. Representative atropisomers and TDG-enabled C-H functionalization.

In recent years, transition metal-catalyzed enantioselective C−H functionalization has emerged as an efficient protocol for atropisomeric synthesis.[12] In this context, Yu performed groundbreaking investigations into the construction of point

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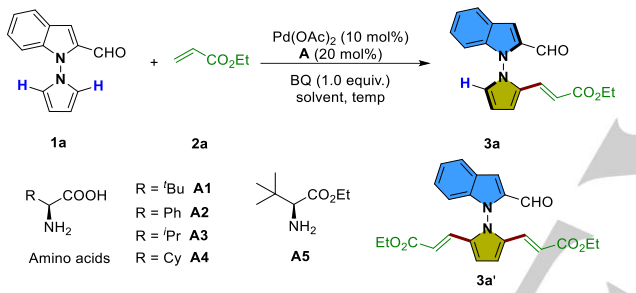
chirality through the use of palladium-catalyzed transient directing group (TDG)-enabled C-H functionalization.[13] Recently, Shi pioneered the atroposelective construction of C-C biaryl atropoisomers using tert-leucine as their TDG.[14] Using this strategy, Shi, Ackermann and et al. were able to access C-C or C–N atropoisomers in a site-specific and enantioselective fashion via the C−H bond functionalization of arenes or alkenes (Scheme 1 B).[15] However, the activation of indole or pyrrole rings using this strategy was unsuccessful. This is unfortunate as atropisomers of indoles and pyrroles are becoming increasingly popular building blocks due to their specific structural and electronic properties.[16] Encouraged by the recent advances and known drawbacks of enantioselective C-H activation, we herein describe a convenient approach for the enantioselective synthesis of N−N atropisomers via a Pd-catalyzed C−H functionalization of pyrroles or indoles using a TDG strategy (Scheme 1C). Using this strategy, various N−N indole-pyrrole or bisindole atropisomers were produced in good yields and with high enantioselectivities via alkenylation, alkynylation, allylation, or arylation reactions. To the best of our knowledge, the atroposelective metal-catalyzed C−H bond activation of pyrroles remains unprecedented.[17]

Table 1. Optimization of the reaction conditions.[a]



Entry	A	Solvent	Oxidant	Yield [%][b]	Ee [%][c]
1	**A1**	HFIP	BQ	7	99
2	**A1**	TFE	BQ	25	97
3	**A1**	toluene	BQ	20	91
4	**A1**	AcOH	BQ	55	99
5	**A1**	HFIP/AcOH = 1:1	BQ	72	99
6	**A1**	HFIP/AcOH = 4:1	BQ	77	99
7	**A1**	TFE/AcOH = 4:1	BQ	70	98
8	**A2**	HFIP/AcOH = 4:1	BQ	15	26
9	**A3**	HFIP/AcOH = 4:1	BQ	32	91
10	**A4**	HFIP/AcOH = 4:1	BQ	40	93
11	**A5**	HFIP/AcOH = 4:1	BQ	42	97
12	**A1**	HFIP/AcOH = 4:1	AgTFA	49	93
13	**A1**	HFIP/AcOH = 4:1	Ag_2CO_3	45	99
14[d]	**A1**	HFIP/AcOH = 4:1	BQ	47	99
15[e]	**A1**	HFIP/AcOH = 4:1	BQ	35	99
16[f]	**A1**	HFIP/AcOH = 4:1	--	5	99
17[g]	**A1**	HFIP/AcOH = 4:1	BQ	50	99
18[h]	**A1**	HFIP/AcOH = 4:1	BQ	81	90
19[i]	**A1**	HFIP/AcOH = 4:1	BQ	30	99

[a] Reaction conditions:**1a** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), amino acid (20 mol %), BQ (1.0 equiv.), solvent (1.0 mL) under air at 60 °C (oil bath) for 16 h. [b] Isolated yields of **3a**. [c] Ee values of **3a** was determined by HPLC analysis. [d] 0.2 Equiv. of BQ under O_2 atmosphere. [e] 0.2 Equiv. of BQ in the air. [f] Under N_2 atmosphere. [g] Under 5 mol% $Pd(OAc)_2$ and 10 mol% **A1**. [h] Reaction was performed at 80 °C for 16 h. [i] **2a** (0.3 mmol) was used, isolated product **3a**: 30%, **3a'**: 54%.

Results and Discussion

Initially, a prochiral aldehyde with an N-N bond axis (**1a**) and ethyl acrylate (**2a,** 1.5 equiv.) were selected as model substrates. The pair were then reacted in HFIP at 60 ℃ in the presence of 10 mol% $Pd(OAc)_2$ and 20 mol% L-tert-leucine (**A1**), with 1.0 equivalent 1,4-benzoquinone (BQ) being used as the oxidant. Although only a 7% yield of the desired product (**3a)** was obtained, enantioselective control of the reaction was found to be as high as 99% (Table 1, entry 1). Encouraged by these results, we investigated the solvent effect and found that a mixture of HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) and AcOH (volume ratio 4:1) significantly improved the yield and gave the best results (77% yield, 99% ee, entry 6), whereas TFE (entry 2), toluene (entry 3), AcOH (entry 4), and other combinations of mixed solvents (entries 5 and 7) produced inferior results. Next, we evaluated the effect of different chiral amino acids (entries 8-11). The results showed that the use of L-tert-leucine (**A1)** as a TDG produced a product with a better yield and ee value when compared to products produced with the other transient directing groups (L-phenylglycine (**A2**), L-valine (**A3**), L-cyclohexylglycine (**A4**), and L-tert-Leucine methyl ester (**A5**)). Furthermore, the choice of oxidant is also crucial for this reaction. BQ was the most efficient oxidant used, and replacing BQ with other silver salts resulted in significantly reduced yields (entries 12-13). A reduced yield was also observed when the reaction was run under an atmosphere of O_2 or air in the presence of a catalytic amount of BQ (entries 14-15). Only trace amount of product **3a** was obtained when benzoquinone was omitted as the oxidant (entry 16). Lower catalyst loadings of 5 mol% $Pd(OAc)_2$ and 10 mol% amino acid **A1** enabled product isolation at a 50% yield and with 99% ee even extended the reaction time to 30 hours (entry 17), and **1a** was recovered in 30% yield. It should also be noted that increasing the reaction temperature to 80 °C improved the yield of **3a** to 81%, but the enantioselectivity was significantly reduced (entry 18). Interestingly, by increasing the amount of ethyl acrylate (**2a**), the product of the double C−H functionalization of pyrrole (**3a'**) was obtained at a 54% yield, while the yield of product **3a** was greatly reduced (30%) (entry 19).

Having established the optimal reaction conditions, the generality of this selective C-H olefination reaction could now be explored. First, the scope of the useable indole framework of the aldehyde was examined (Scheme 2). Substrates bearing methoxy, methyl, aryl, or halogen substituents (chloro, fluoro) at the 4-(**3i**), 5-(**3b-3h**), 6-(**3j, 3k**), or 7-position (**3l**) of the indole moiety reacted smoothly to furnish the desired N-N indole-pyrrole atropisomers at a 50−88% yield, and with 99% enantioselectivity. Moreover, the inclusion of the C3-functionality on the indole was also successful, affording N-N atropisomer **3m** with a 57% yield and a 97% ee. Next, various alkenes were used to construct N-N indole-pyrrole atropisomers. Generally, this strategy is applicable to various acrylates for the synthesis of N-N atropisomers in high yields and with good enantioselectivities. Not only vinyl esters (**3a**–**3q**), but also aryl alkene underwent C-H activation efficiently to give the N-N atropisomer (**3u**) in 57% yield and with 99% ee. In addition, acrylamide was also found to be a suitable partner, and the

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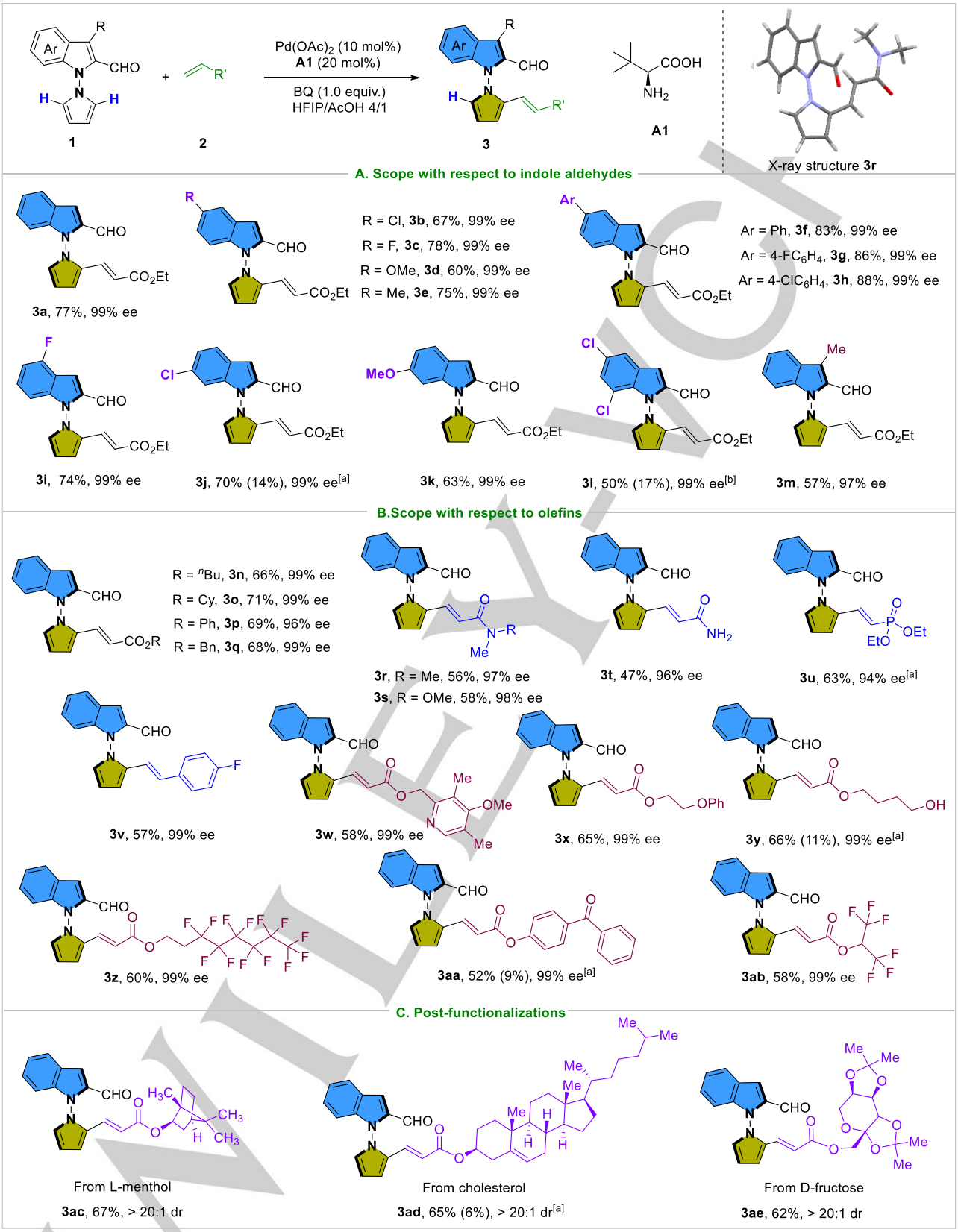

Scheme 2. Substrate scope for prochiral aldehydes and olefins, reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), L-tert-leucine **A1** (20 mol%), BQ (1.0 equiv.), HFIP/AcOH 4/1 (1.0 mL) under air at 60 °C (oil bath) for 16-24 h. [a] 2.0 Equiv. olefin was used, numbers in parentheses refers to double C-H functionalization products. [b] Number in parentheses refers to recovered starting material.

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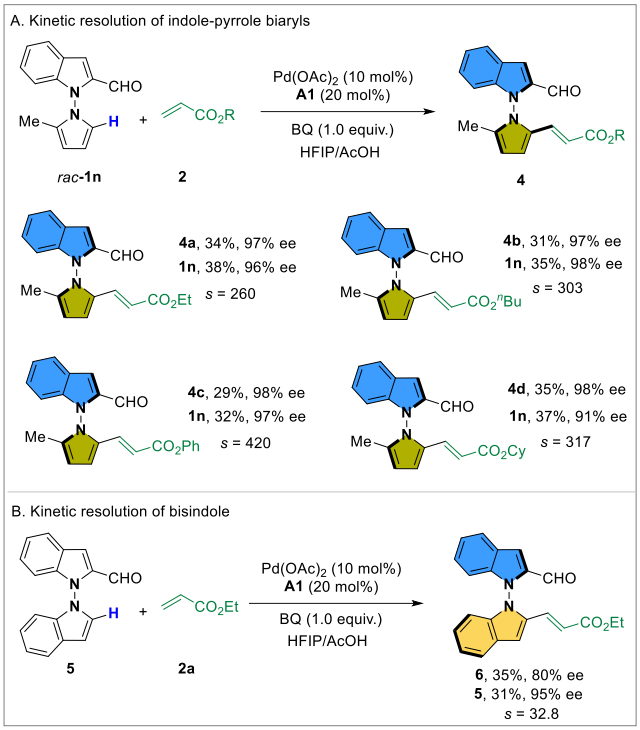
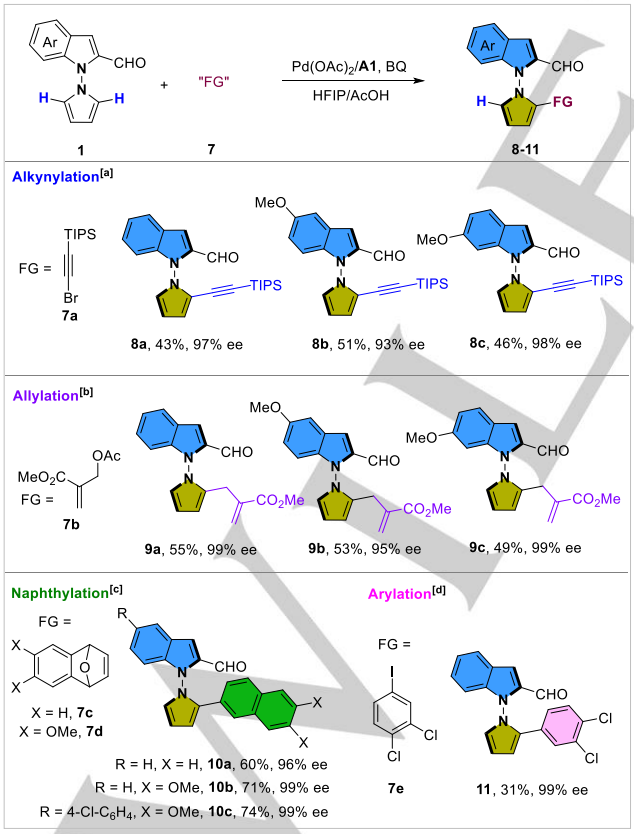


Scheme 3. Kinetic resolution of racemic N−N biaryls, reaction conditions: **4** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), L-tert-leucine **A1** (20 mol %), BQ (1.0 equiv.), HFIP/AcOH 4/1 (1.0 mL) under air at 60 °C (oil bath) for 16 h.



Scheme 4. Enantioselective C−H activation of pyrroles with different electrophiles, reaction conditions: [a] **1** (0.10 mmol), **7a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), **A1** (30 mol%), AgOAc (2.0 equiv.), KH_2PO_4 (1.0 equiv.), HOAc (1.0 mL) at 40 °C (oil bath) for 24 h. [b] **1** (0.10 mmol), **7b** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), **A1** (20 mol%), BQ (1.0 equiv.), HFIP/HOAc = 4:1 (1.0 mL) under air at 60 °C (oil bath) for 16 h. [c] **1** (0.10 mmol), **7c** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), **A1** (30 mol%), $AdCH_2CO_2H$ (2.5 equiv.), $^nPrCO_2Na$ (2.0 equiv.), TFE/HOAc = 9:1 (1.0 mL) under air at 60 °C (oil bath) for 18 h. [d] **1** (0.10 mmol), **7d** (0.2 mmol), $Pd(TFA)_2$ (10 mol%), **A1** (30 mol%), AgTFA (2.0 equiv.), TFA (3.0 equiv.), HFIP (1.0 mL) under air at 60 °C (oil bath) for 24 h.

desired product was obtained in moderate yield and with excellent enantioselectivity (**3r-3t**). The absolute configuration was confirmed by the single-crystal X-ray analysis of **3r** (CCDC 2225140).[18] Importantly, substrates with free hydroxyl (**3y**) or amine group (**3t**) were compatible with this reaction, although the yield and ee were slightly reduced when the amine group was present. Furthermore, ethyl alkenyl phosphate afforded N-N atropisomer **3u** at a 63% yield and with 94% enantioselectivity. Moreover, a variety of functional or bioactive moieties could be installed via vinyl linkers. Using this method, the installation of a 2-phenoxyethyl acrylate (**3x**, monomer in multifunctional and shape memory polymers), 4-benzoylphenyl acrylate (**3aa**, photoinitiator scaffold), perfluorohexylethyl acrylate group (**3z**, **3ab**), or pyridinemethanol group (**3w**) into the substrate was possible, and the products were created with good yields with excellent enantioselectivities. To further demonstrate the utility of this strategy, some olefins derived from the core structures of natural products (L-menthol, **3ac**; cholesterol, **3ad**; and D-fructose, **3ae**) were employed as coupling partners. The corresponding products were again obtained in excellent yields and with outstanding diastereoselectivity.

To further verify the universality of the reaction, we investigated the kinetic resolution (KR) of racemic N−N biaryls. As shown in Scheme 3A, the kinetic resolution could tolerate different substituted alkenes **2** to produce the desired N−N atropisomers **4a-4d,** bearing sterically more demanding substituents in 29−35% yield and with 97−98% ee. Furthermore, the enantioenriched starting material **1n** was recovered in 91−98% ee, thereby giving excellent selectivity factors (*s* up to 420). Moreover, racemic N−N bisindole **5** could also be resolved, the corresponding bisindole **6** can be obtained in 80% ee, and unreacted **5** was recovered simultaneously in yield of 31% with 95% ee. (Scheme 3B).

The feasibility of our design was investigated further through the reaction of **1a** with different electrophiles in the hopes of achieving divergent synthesis. To our delight, various N−N indole-pyrrole atropisomers were produced with good yields and high enantioselectivities via alkynylation, allylation, naphthylation, or arylation reactions. As shown in Scheme 4, the alkynylated products **8a-8c** were obtained with yields of 43−51% and with ee values of 93−98% when AgOAc was used as the oxidant in HOAc. The reaction could also be conducted smoothly using the allylic reagent **7b** to give chiral allylation product **9** at a 49−55% yield and with a 95−99% ee via TDG-enabled enantioselective C−H allylation. The atroposelective C−H arylation could be achieved by two different strategies: 1) Pd-catalyzed atroposelective C−H naphthylation with 7-oxabenzonorbornadienes for the preparation of an N−N indole-pyrrole atropisomers **10a-10c** with excellent enantioselectivities, or 2) direct asymmetric C−H arylation with aryl iodide for the construction of a more general arylation product, although with a relatively lower yield (**11**, 31% yield, 99% ee).

Subsequently, we demonstrated applications of the Pd-catalyzed atroposelective C-H olefination by performing a gram-scale reaction of **1a** with **2a**. The resulting N-N atropisomer **3a**

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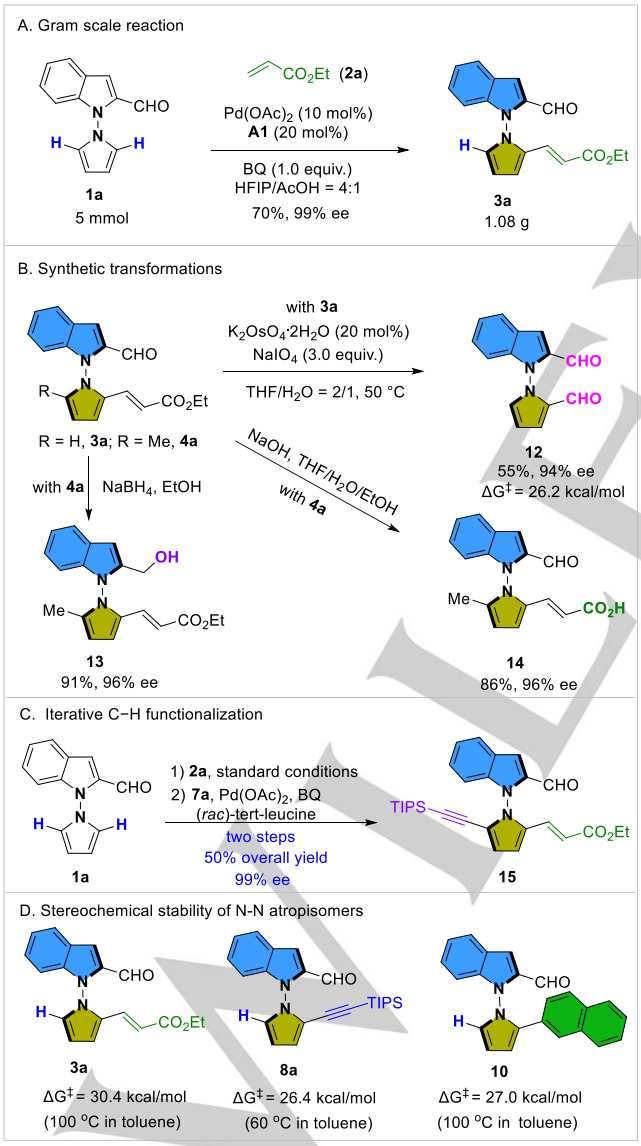
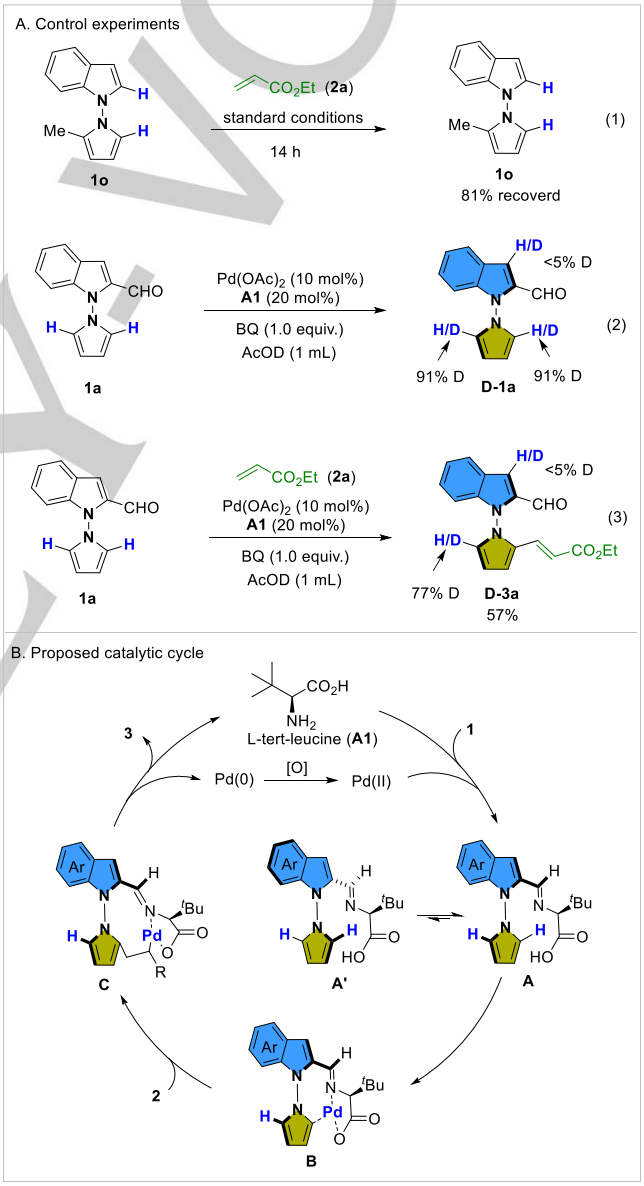
was obtained in 70% isolated yield and 99% ee (Scheme 5A). Further derivatization of the N-N atropisomers are illustrated in Scheme 5B. Under oxidative conditions, the double bond of **3a** was readily converted to the aldehyde group to afford diarylaldehyde N-N atropisomer **12** in 55% yield with a slightly reduced enantioselectivity (94% ee). The racemization barrier of **12** was measured to be 26.2 kcal/mol (see the Supporting Information for details), which may indicate that partial thermal racemization of **12** was due to the low rotational energy barrier. Moreover, tetrasubstituted N-N atropisomer **5a** could be selectively reduced to produce alcohol **13** under mild conditions without a loss in enantioselectivity and ester hydrolysis to carboxylic acid **14** in good yield. We next sought to combine controllable C−H functionalization of pyrroles into an iterative process (Scheme 5C). We showed that we can use the palladium-catalyzed TDG methodology to functionalize different positions of the prochiral pyrrole by continuous olefination and alkynylation to afford **15** in 50% overall yield and 99% enantioselectivity.



Scheme 5. Gram-scale reaction, synthetic transformations and stereochemical stability of N-N atropisomers.

Stereochemical stability is crucial if these N-N atropisomers are to be implemented in pharmaceutical studies and ligand design. Therefore, the stability of these new indole-pyrrole atropisomers was investigated (Scheme 5D). The er value for **3a** decreased to 76:24 after stirring for 7 h at 100 °C in toluene. Based on this, the barrier to the rotation of **3a** was determined to be 30.4 kcal/mol, which is categorized as the class-3 atropisomer based on LaPlante and Edwards's atropisomer stability classification system and provided sufficient stability for further pharmaceutical studies.[19] In comparison, alkynylation atropisomer **8a** and **10** exhibited less steric hindrance around the N-N axis, and the measured rotational energy barriers were reduced to 26.4 kcal/mol and 27.0 kcal/mol, respectively.



Scheme 6. Control experiments and proposed catalytic cycle.

To gain insights into the mechanism, several experiments were conducted (Scheme 6A). First, we performed the reaction with starting material **1o** without aldehyde moiety, the desired product was not got under the standard conditions with 81% **1o**

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recovered after 14 hours, which showed the importance of the CHO group and the real formation of the TDG. Deuterium-labeling studies were next carried out using deuterated solvents. The reaction of **1a** in AcOD with omission of ethyl acrylate for 14 h led to 91% deuteration at the 2-position of pyrrole ring. Similarly, 77% deuterium incorporation was observed when using ethyl acrylate **2a** as the coupling partner. These results clearly indicated that the C-H cleavage of pyrrole occurred.

Based on these results, and in the literature on TDG-enabled C-H functionalizations,[15g-15i] a plausible mechanism was proposed. As shown in Scheme 6B, *rac*-**1** would reversibly react with L-tert-leucine (**A1**) to generate the imines **A** and **A'**. The C-H activation of **A** is preferred owing to the steric interaction, leading to an axially stereoenriched palladacycle intermediate **B**. Migratory insertion of olefin **2** into palladacycle **B** afforded intermediate **C**. *β*-H Elimination and in situ hydrolysis of the imine would afford the N-N atropisomers **3** with the formation of Pd(0) species and regeneration the chiral amino acid TDG. Oxidation of the Pd(0) by BQ oxidant regenerate Pd(II) and closed the catalytic cycle.

Conclusion

In conclusion, we have developed an efficient and practical method to construct a new class of N-N atropisomers via the Pd-catalyzed atroposelective C-H functionalization of pyrroles or indoles. The method presented in this study allowed for a wide variety of atropisomers with chiral N-N axes to be produced via alkenylation, alkynylation, allylation, and arylation reactions, with most showing good yields and high enantioselectivities. This TDG-enabled C-H functionalization strategy also allows for the highly selective, iterative functionalization of pyrroles, simplifying the formation of valuable complex N-N atropisomers.

Acknowledgements

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Keywords: asymmetric catalysis · atropisomerism · TDG · palladium · pyrroles

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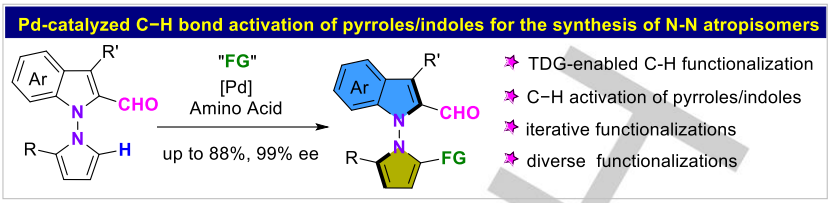
RESEARCH ARTICLE

Asymmetric Catalysis

*Wang Yao,† Chuan-Jun Lu,† Li-Wen Zhan, Yi Wu, Jia Feng, and Ren-Rong Liu*_____ **Page – Page**

Enantioselective Synthesis of N-N Atropisomers by Palladium-Catalyzed C−H Functionalization of Pyrroles



Enantioselective synthesis of N-N indole-pyrrole and bisindole atropisomers was achieved by a palladium-catalyzed TDG-enabled C−H functionalization. A wide variety of the N-N atropisomers were produced in good yields with excellent enantioselectivities by C−H alkenylation, alkynylation, allylation or arylation reactions.