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A New Saddle-Shaped Aza Analog of Tetraphenylene: Atroposelective Synthesis and Application as a Chiral Acylating Reagent

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ABSTRACT: (Z)-7-Aryl-5-acyldibenzo[e.g][1,4]diazocin-6(5H)-one, a unique saddle-shaped bridged biaryl containing synchronized aryl-aryl and N-aryl stereogenic axes, was constructed for the first time in good yields with up to 96% ee. The three-component coupling reaction involving aryl iodide, 2,2'-disiocano-1,1'-biphenyl, and carboxylate sews the eight-membered ring atroposelectively through palladium-catalyzed double isocyanide insertion followed by carboxylate participating in reductive elimination and acyl transferring amide formation. The N-acyl amide moiety in this twisted and atropisomERICally stable (ΔG approximately 35.9 kcal/mol) scaffold can serve as a recyclable acylating reagent to acylate racemic primary amines through kinetic resolution in moderate enantioselectivities.

Keywords: diazocin, tetraphenylene analog, atroposelective synthesis, double isocyanide insertion, palladium catalysis

Introduction

Tetraphenylene consists of four phenyl units that are ortho-annulated in an extraordinarily stable saddle-shaped geometry, and the inversion barrier is as high as 80.6 kcal/mol between the two conformers (Figure 1a, I).⁴ The scaffold gains chirality when substituted unsymmetrically. The preparation and related applications of chiral tetraphenylene derivatives have been widely studied, especially by Wong and coauthors.⁵-⁶ However, the enantiomers are accessed mainly by resolution of the diastereomeric derivatives, and there are only few reports on enantioselective synthesis of substituted tetraphenlenes⁷-⁸ and other similar saddle-shaped chiral molecules.⁹-¹⁰ Simplifying the tetraphenylene framework by replacing one or two of the phenyl ring(s) with aza functionalities would generate aza analogs II-IV, which still prefer the saddle-shaped orientation. Although the energy barriers for inverting these aza analogs are significantly lower than those for tetraphenylene, they are still atropisomERICally stable enough (31–40 kcal/mol) to tolerate routine conditions for asymmetric catalysis.¹¹ More importantly, methods to access these skeletons will be much easier, rendering more opportunities for enantioselective synthesis. Very recently, Zhang developed a novel preparation of racemic or diastereomeric derivatives of 9,10-dihydrotribenzo[b,d,f]azocine (II) through Pd-catalyzed cross coupling of 2-iodobiphenyls with 2-bromobenzenamines.¹² Both aza analogs III and IV are stable chiral molecules with multiple synchronized stereogenic axes.¹³-²⁶ But optically pure enantiomers are not available catalytically. Undoubtedly, designing new analogs such as V and exploring catalytic enantioselective synthesis of this unique class of aza saddle-shaped architectures is of great importance for the development of new chiral ligands, catalysts, and reagents.

[Figure of saddle-shaped structures and energy barriers]

b) Hypotheses for the synthesis eight-membered ring through Pd-catalyzed double isocyanide insertion

c) Construction of a new chiral aza-saddle-type framework by double isocyanide insertion (this work)
Figure 1. Saddle-shaped tetraphenylene and its aza-analogs

By trapping the imidoyl palladium intermediate with an intramolecular functionality following isocyanide insertion to a Pd(II) species, a variety of 5–7-membered nitrogen-containing heterocycles could be generated.\(^1\)–\(^6\) In addition, N-heterocycles bearing central and planar as well as axial chirality have been successfully constructed by applying this strategy, opening an avenue for isocyanide in transition-metal-catalyzed asymmetric synthesis.\(^7\)–\(^10\) Particularly, the chemistry of using 2-isocyno-1,1'-biphenyl for the synthesis of 6-arylenanthridine inspires the hypothesis that a structurally similar 2,2'-disiocynyolo-1,1'-biphenyl would proceed through an unprecedented double isocyanide insertion followed by termination with an intermolecular nucophile (Figure 1b).\(^11\) As a result, an eight-membered aza bridged biaryl, mostly likely possessing a comfortable saddle-shaped geometry, could be formed. However, two independent C-H activations after one isocyanide insertion are foreseeable side reactions. We report herein the first enantioselective synthesis of a saddle-shaped aza analog of tetraphenylene \(V\) and its primary application serving as a novel acylating reagent of primary amines through kinetic resolution (Figure 1c).

Results and Discussion

For the investigation, 2,2'-diisocyano-1,1'-biphenyl (11), a bench-stable white solid, was prepared for the first time in good yield from the corresponding diformamide by dehydration.\(^12\)–\(^14\) Initial attempts to verify the hypothesis in reactions involving 2,2'-disiocyno-1,1'-biphenyl (11), iodobenzene (2–1), and aryl boronic acid or olefin catalyzed by Pd(dppf)Cl\(_2\) excluded double phenanthridine formation as a side reaction; nevertheless, the desired eight-membered N-heterocycle was not obtained. No new product was detectable by TLC analysis, although isocyanide 1-1 was consumed. Gratifyingly, an unexpected pivalate-incorporated product was isolated when using CsOPiv as a base. The product was identified as (Z)-7-phenyl-5-pivaloyldibenzo[\(e,g\)][1,4]diazocin-6(5H)-one 3–1, a new saddle-shaped aza analog of tetraphenylene (vide infra), formed most likely through acyl transferring amide formation (entry 1, Table 1). Encouraged by the results, a range of chiral ligands was evaluated in the enantioselective synthesis of 3–1 in the presence of Pd(OAc)\(_2\), as the catalyst. Chiral phosphoramidite ligands, successfully applied in our previous Pd-catalyzed asymmetric imidoylate annulation, could not even drive the reaction to occur (see SI for details).\(^15\)–\(^18\) Taking into account the effectiveness of dppf in forming racemic 3–1, structurally diversified and commercially available bidentate phosphorus Josiphos (L1–L10) was then tested. It is intriguing that when both of the substitutions on the phosphine are aryl groups (R, \(R'\) = Ar), such as L1, 3–1 that could be obtained in 52% yield, no enantiomeric bias occurred at all. In contrast, when both R and \(R'\) are alkyl groups (L10), enantiomer enriched 3–1 (75% ee) is produced, but in trace amounts (entry 11, Table 1). As expected, L2 with mixed substitutions (R = Cy, \(R'\) = Ph) is effective in product formation, as well as in asymmetric induction (37% yield, 42% ee, entry 3). Then, the optimal ligand L8 was identified, although the result was still not satisfactory (26% yield, 81% ee, entry 9). Ferrocene-based heteronuclear bidentate ligands L11–L13 with cyclic phosphines also failed to promote the current three-component coupling in acceptable yields, even after varying the solvent and altering the time for the addition of isocyanide via a syringe pump (entries 12–20). Next, by changing the catalyst to Pd\(_2\)(dba)\(_3\)-CHCl, in the presence of L2, the enantioselectivity increases surprisingly to 93% ee, but the yield is still low (entry 21). To our delight, 3–1 can be obtained in 73% yield with 90% ee by switching the ligand back to L8 (entry 22). Finally, the optimal conditions are identified as outlined in entry 23.

Table 1. Optimization of the reaction conditions\(^a\)

| entry | \(\beta\) | [Pd] | L | solvent | yield (%) | ee (%) |
|-------|--------|------|---|---------|-----------|-------|
| 1     |       | Pd(dppf)Cl\(_2\) |   | toluene | 70        |       |
| 2     |       | Pd(OAc)\(_2\) | L1 | toluene | 52        | 0     |
| 3     |       | Pd(OAc)\(_2\) | L2 | toluene | 37        | 42    |
| 4     |       | Pd(OAc)\(_2\) | L3 | toluene | 65        | 12    |
| 5     |       | Pd(OAc)\(_2\) | L4 | toluene | 34        | 0     |
| 6     |       | Pd(OAc)\(_2\) | L5 | toluene | 0         |       |
| 7     |       | Pd(OAc)\(_2\) | L6 | toluene | 46        | 30    |
| 8     |       | Pd(OAc)\(_2\) | L7 | toluene | 7         | -25   |
| 9     |       | Pd(OAc)\(_2\) | L8 | toluene | 26        | 81    |
| 10    |       | Pd(OAc)\(_2\) | L9 | toluene | 11        | 30    |
| 11    |       | Pd(OAc)\(_2\) | L1 | toluene | 0         | 75    |
| 12    |       | Pd(OAc)\(_2\) | L11| toluene | 34        | -75   |
| 13    |       | Pd(OAc)\(_2\) | L12| toluene | 8         | 84    |
| 14    |       | Pd(OAc)\(_2\) | L13| toluene | 0         |       |
| 15\(^b\) |       | Pd(OAc)\(_2\) | L12| xylene | <=5        | 78    |
| 16\(^b\) |       | Pd(OAc)\(_2\) | L12| xylene | <=5        | 78    |
| 17\(^b\) |       | Pd(OAc)\(_2\) | L12| mesitylen | <=<        | 73    |
| 18\(^b\) |       | Pd(OAc)\(_2\) | L12| PhCF\(_3\) | 5         | 55    |
| 19\(^b\) |       | Pd(OAc)\(_2\) | L12| dioxane | trac      | e     |
| 20\(^b\) |       | Pd(OAc)\(_2\) | L12| CH\(_2\)CN | 0        |       |
| 21\(^b\) |       | Pd\(_2\)(dba)\(_3\)-CHCl | L12 | toluene | 20        | 93    |
| 22\(^b\) |       | Pd\(_2\)(dba)\(_3\)-CHCl | L8 | toluene | 73        | 90    |
| 23\(^b\) |       | Pd\(_2\)(dba)\(_3\)-CHCl | L8 | toluene | 74        | 93    |

\(^a\) Reaction conditions: \(\beta\) = 50 bar, \(\beta\) = 150°C, \(\beta\) = 20 h.
Following the identification of the optimal reaction conditions, the scope of aryl iodides was first explored with the other two reaction components unchanged. As shown in Scheme 1, aryl iodides bearing a wide range of substituents on the para position, including Me, OMe, halogen, COOEt, CN, and CF₃, reacted smoothly to give corresponding products 3–2 to 3–12 in moderate to good yields (52–87%) with excellent enantioselectivities (86–95%) ee. However, 1-iodo-4-nitrobenzene was less compatible in the reaction, delivering 3–13 in low yield with 72% yield, ee. In general, meta-substituted aryl iodides were also suitable substrates to initiate the tandem process with slightly diminished but still good enantioselectivities (mostly 89–92% ee). Substitution at the ortho position of iodides was apparently disadvantageous for enantioselectivity. For example, 3–22 was formed with 81% yield, ee, while the corresponding meta- and para-analogs 3–14 and 3–2 were obtained in 90% ee and 93% ee, respectively. Sterically hindered 1-naphthyl iodide participated in the reaction with acceptable yield but low ee (3–24). It is notable that when the reaction was run in 1 mmol scale, 3–1 was isolated with comparable 65% yield and 92% ee (v.s. 74% yield and 93% ee in 0.1 mmol scale). When bromobenzene was used in place of iodobenzene under otherwise identical conditions, the desired product 3–1 was not detected.

Scheme 1. Scope of aryl iodide

Next, the scope of carboxylic acids applicable to the reaction was investigated by combining carboxylic acid and Cs₂CO₃ if the corresponding cesium carboxylate was not commercially available (Scheme 2). It was found that acetate was a poor nucleophile in the reaction (33% yield, 3–28), probably due to its sluggishness upon reductive elimination. The steric bulkiness of aliphatic acids was proven to be beneficial for the reaction, and adamantine-1-carbonylated 3–30 was obtained in 76% yield with 91% ee. For- to six-membered cyclic carboxylates could also serve as effective nucleophiles to terminate the domino process in good yields with excellent ee (3–31 to 3–33). X-ray diffraction analysis of crystallized 3–31 clearly depicted its absolute saddle-shaped configuration. However, the N-H free amide derivative 3–34 generated through in situ hydrolysis was isolated when using benzoic acid as the nucleophile.

Scheme 2. The scope of carboxylates
Scheme 3. Scope of biaryl diisocyanides

- Reaction conditions: 2-1 (0.12 mmol), Pd(dba)$_2$-CHCl$_2$ (2.5 mol%) L8 (0.10 mmol), RCOOH (0.10 mmol), Cs$_2$CO$_3$ (0.10 mmol), 80 °C, in toluene (1 mL) was added to the reaction mixture via a syringe pump within 1 h. The isolated yield ee was determined by HPLC analysis using a chiral stationary phase.  

- Benzonic acid was used.

Finally, the compatibility of substituted 2,2'-diisocynano-1,1'-biphenyls (1) was investigated (Scheme 3). When biaryl diisocyanides containing symmetrical substituents, including Me, OMe, COOMe, and F, at the para positions were coupled with iodobenzene and pivalate, the yields and enantioselectivities were basically maintained (3–35 to 3–38). However, in the case of chlorinated derivative (3–39) a significant amount of hydrolyzed byproduct was found. When 2,2'-diisocynano-1,1'-biphenyl substituted with more electron deficient CF$_3$ was applied, product 3–40 was fully hydrolyzed in 76% isolating yield with 94% ee. Methyl- and methoxy-substituted derivatives (3–41 and 3–42) were obtained with slightly lower ee. Unfortunately, substituents at the ortho-position of the isocyanate group severely deteriorated the enantioselectivity (3–44 and 3–45); however, the yields for product formation were unaffected. It is worth mentioning that the X-ray diffraction analysis shows that the configuration of 3–44 is opposite to other products. It was not surprising that the unsymmetrical biaryl disiocyanide was nonregioselective upon the initial isocyanide insertion, leading to a 1:1 inseparable mixture of isomers (3–46 and 3–47).

Scheme 3. Scope of biaryl diisocyanides

- Reaction conditions: 2-1 (0.12 mmol), Pd(dba)$_2$-CHCl$_2$ (2.5 mol%) L8 (0.10 mmol), Cs$_2$CO$_3$ (0.10 mmol), 80 °C, in toluene (1 mL) was added to the reaction mixture via a syringe pump within 1 h. The isolated yield ee was determined by HPLC analysis using a chiral stationary phase.

It is worth mentioning that a small amount of byproduct, the N-H free amide derivative generated through hydrolysis, could always be detected during the reaction. Therefore, a one-pot coupling/hydrolysis procedure was conducted by the addition of HCl solution (1.0 M, 1 mL) after the standard coupling reaction. Fully hydrolyzed N-H free amide 3–34 was obtained in 95% yield with 92% ee (Scheme 4). Interestingly, treatment of amide 3–34 with NaH, followed by addition of the acylation reagent PivCl, gave 3–41 in 94% yield without loss of enantioselectivity. By applying this protocol, products that could not be produced under the standard coupling reaction conditions could be accessed, which greatly expanded the product diversity. The absolute configuration of compound 3–48 was also confirmed by X-ray crystal diffraction.

Scheme 4. One-pot synthesis and transformations of 3–34
The reaction is initiated by oxidative addition of phenyl iodide to Pd(0) to afford the phenyl palladium(II) species. Then, coordination and migratory insertion of the first isocyanide moiety of 1–1 to Pd(II) generates imidoyl palladium species INT-I, followed by coordination of the second isocyanide moiety to the Pd center. The second migratory insertion of the isocyanide group yields intermediate INT-III, which undergoes reductive elimination to afford intermediate INT-IV. Finally, migration of the Piv group to N delivers the product.\(^{43}\) To elucidate the origins of the enantioselectivity, DFT calculations of the enantiosomeric product-formation pathways were conducted (Figure 2b and 2c). The formation of the enantiomer involves a chirality generating isocyanide-insertion step via TS-\(\Delta\) and TS-\(S\). Comparing the determining steps (TS-\(\Delta\) versus TS-\(S\)), the formation of the major enantiomer is 3.6 kcal/mol more favorable than that of the minor enantiomer, which corroborated the excellent enantioselectivities in experimental observations. For TS-\(\Delta\) and TS-\(S\), the distortion-interaction analysis\(^{43-47}\) reveals that the major contribution of activation energy (\(\Delta\DeltaE_{act}\)) is from the distortion of the palladium catalyst and the chiral ligand (Figure 2b), probably because of the coordination distance and dihedral angle of the chiral ligand to Pd center.

A plausible reaction mechanism is proposed in Figure 2a. The reaction is initiated by oxidative addition of phenyl iodide to Pd(0) to afford the phenyl palladium(II) species. Then, coordination and migratory insertion of the first isocyanide moiety of 1–1 to Pd(II) generates imidoyl palladium species INT-I, followed by coordination of the second isocyanide moiety to the Pd center. The second migratory insertion of the isocyanide group yields intermediate INT-III, which undergoes reductive elimination to afford intermediate INT-IV. Finally, migration of the Piv group to N delivers the product.\(^{43}\) To elucidate the origins of the enantioselectivity, DFT calculations of the enantiosomeric product-formation pathways were conducted (Figure 2b and 2c). The formation of the enantiomer involves a chirality generating isocyanide-insertion step via TS-\(\Delta\) and TS-\(S\). Comparing the determining steps (TS-\(\Delta\) versus TS-\(S\)), the formation of the major enantiomer is 3.6 kcal/mol more favorable than that of the minor enantiomer, which corroborated the excellent enantioselectivities in experimental observations. For TS-\(\Delta\) and TS-\(S\), the distortion-interaction analysis\(^{43-47}\) reveals that the major contribution of activation energy (\(\Delta\DeltaE_{act}\)) is from the distortion of the palladium catalyst and the chiral ligand (Figure 2b), probably because of the coordination distance and dihedral angle of the chiral ligand to Pd center.

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Figure 2. Mechanistic studies.

### Conclusion

In summary, we developed a novel three-component coupling reaction involving aryl iodide, 2,2'-diisocyanato-biphenyl, and carboxylate to construct a unique saddle-shaped azanalog of tetraphenylene for the first time in good yields and excellent enantioselectivities. The reaction proceeds through palladium-catalyzed double isocyanide insertion followed by carboxylate participating in reductive elimination and acyl transferring amide formation. The N-acyl amide moiety in this twisted and atropisomerically stable ($\Delta G \approx 35.9$ kcal/mol) scaffold can serve as a recyclable acylating reagent to acylate racemic primary amines through kinetic resolution in moderate enantioselectivities.

### Supporting Information

Supporting information is available online and includes experimental procedure, nuclear magnetic resonance (NMR) spectra, high performance liquid chromatography (HPLC), X-ray crystallographic data, and DFT calculation. Correspondence and requests for materials should be addressed to the corresponding author.

### Conflict of Interest

The authors declare no competing financial interest.

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![Diagram](image-url)

> **50 examples, up to 95% yield, 96% ee**

- the first asymmetric double isocyanide insertion
- a new aza-saddle-type framework
- excellent enantioselectivity
- a new chiral recyclable acylating reagent