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Catalytic Asymmetric Arylation of α-Aryl-α-diazoacetates with Aniline Derivatives

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Supporting Information

ABSTRACT: The asymmetric arylation of diazo compounds with aniline derivatives cooperatively catalyzed by an achiral dirhodium complex and a chiral spiro phosphoric acid is reported. The reaction provides a new method for the facile synthesis of α-diarylacetates, versatile building blocks with a diaryl tertiary chiral center, in good yields (up to 95%) with high enantioselectivities (up to 97% ee). Preliminary mechanistic studies suggest that the arylation reaction proceeds via a stepwise process, in which the enantioselectivity is controlled by a chiral spiro phosphoric acid-promoted proton shift in a zwitterionic intermediate. This work represents the first asymmetric intermolecular C(sp^2)−H bond insertion reaction with arenes.

Diaryl tertiary chiral centers are ubiquitous substructures in natural products and pharmaceuticals,[1] such as (+)-sertraline (Zoloft),[1b] (*R*)-tolterodine (Detrol),[1c] podofilox (Condylox),[1d] CDP-840,[1e] and nomifensine[1f] (Figure 1). Therefore,

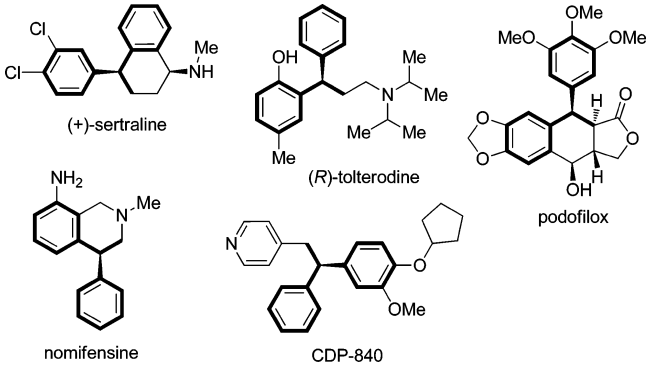
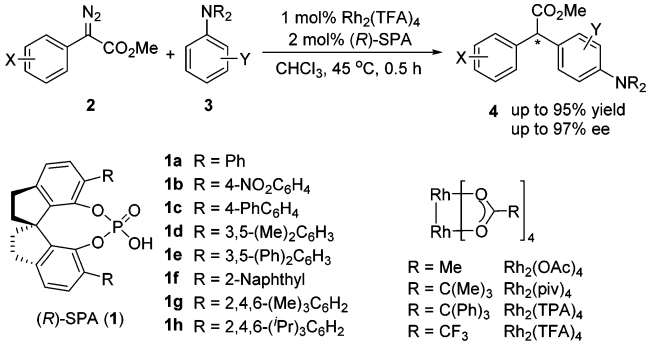


Figure 1. Selected bioactive compounds containing a chiral diaryl tertiary center.

the development of methods for enantioselective synthesis of compounds with this substructure has attracted considerable attention.[2] One possible method is the arylation (formal C(sp^2)−H insertion) of α-aryl-α-diazoacetates with benzene derivatives, which is a straightforward, efficient route to α-diaryl acetates. Although remarkable progress has been made on the nonasymmetric version of the reaction,[3] the asymmetric version remains unknown. Davies et al.[4] investigated the arylation reaction of methyl 2-(4-bromophenyl)-2-diazoacetate with *N*,*N*-dimethylaniline using chiral dirhodium catalysts but obtained only the racemic product. We herein report the enantioselective arylation of α-aryl-α-diazoacetates with aniline derivatives cooperatively catalyzed by dirhodium(II) trifluoroacetate and chiral spiro phosphoric acids (SPAs). This new reaction directly and efficiently provides chiral α-diaryl acetates in good yields (up to 95%) with high enantioselectivities (up to 97% ee) (Scheme 1). Although transition-metal-catalyzed C−H insertion of

Scheme 1. Enantioselective Catalytic Arylation of α-Aryl-α-diazoacetates



carbenoids is a powerful method for C−H functionalization and significant progress has been made in the development of asymmetric C(sp^3)−H insertion reactions,[5] reports of asymmetric C(sp^2)−H insertion reactions are scarce and focus on intramolecular reactions[6] and reactions with indoles,[7] a typical heteroarene. To the best of our knowledge, the reaction reported herein represents the first asymmetric intermolecular C(sp^2)−H insertion reaction with arenes.

We optimized the reaction conditions for the arylation by using methyl 2-diazo-2-phenylacetate (**2a**) and 1-phenylpyrrolidine (**3a**) as substrates (Table 1). The reaction was complete in 30 min when it was conducted at room temperature in the presence of 1 mol % $Rh_2(OAc)_4$ and 1 mol % (*R*)-**1a** as catalysts, and the desired arylation product (**4a**) was obtained in 52% yield with 17% ee, along with the C(sp^3)−H insertion product, methyl 2-phenyl-2-(1-phenylpyrrolidin-2-yl)acetate (20% yield, 0% ee, entry 1). Evaluation of various chiral SPAs revealed that (*R*)-**1g**, which has two 6,6′-di(2,4,6-trimethylphenyl) moieties, gave the highest enantioselectivity (51% ee, entries 2−8). The use of a bulkier dirhodium catalyst, $Rh_2(piv)_4$

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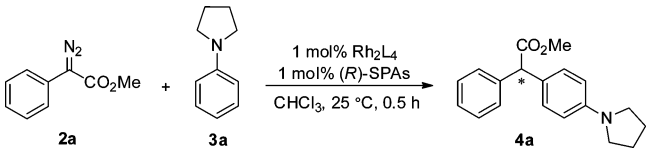
Table 1. Enantioselective Arylation of Methyl 2-Diazo-2-phenylacetate with 1-Phenylpyrrolidine: Optimization of Reaction Conditions



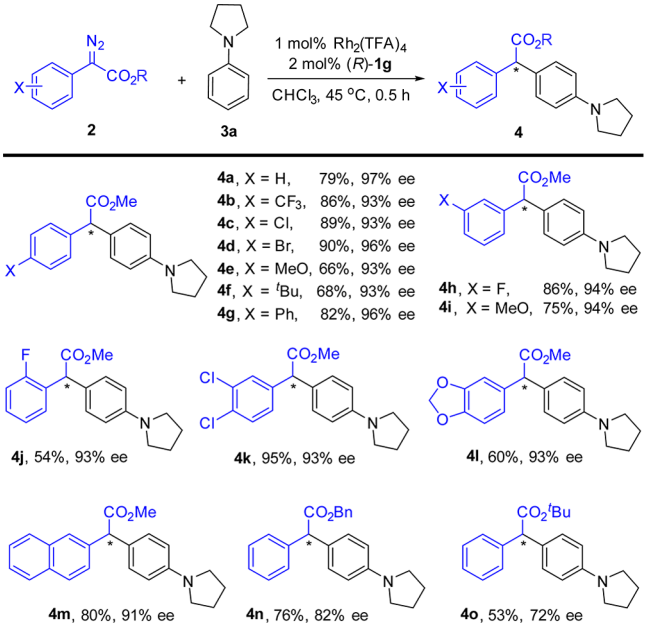
entry[a]	Rh_2L_4	SPAs	yield (%)[b]	ee (%)[c]
1	$Rh_2(OAc)_4$	(*R*)-**1a**	52	17
2	$Rh_2(OAc)_4$	(*R*)-**1b**	34	0
3	$Rh_2(OAc)_4$	(*R*)-**1c**	48	4
4	$Rh_2(OAc)_4$	(*R*)-**1d**	38	8
5	$Rh_2(OAc)_4$	(*R*)-**1e**	46	11
6	$Rh_2(OAc)_4$	(*R*)-**1f**	48	10
7	$Rh_2(OAc)_4$	(*R*)-**1g**	45	51
8	$Rh_2(OAc)_4$	(*R*)-**1h**	42	5
9	$Rh_2(piv)_4$	(*R*)-**1g**	20	10
10	$Rh_2(TPA)_4$	(*R*)-**1g**	66	16
11	$Rh_2(TFA)_4$	(*R*)-**1g**	64	92
12[d]	$Rh_2(TFA)_4$	(*R*)-**1g**	66	95
13[e]	$Rh_2(TFA)_4$	(*R*)-**1g**	55	95
14[f]	$Rh_2(TFA)_4$	(*R*)-**1g**	43	49
15[d,g]	$Rh_2(TFA)_4$	(*R*)-**1g**	79	97

[a]Reaction conditions: Rh_2L_4/SPA/**2a**/**3a** = 0.002:0.002:0.2:0.2 (mmol) in 3 mL of $CHCl_3$ at 25 °C. [b]Isolated yield. [c]Determined by supercritical fluid chromatography using a Chiralcel OJ-H column. [d]At 45 °C. [e]At reflux; reaction time: 5 min. [f]At 0 °C; reaction time: 1 h. [g]Using 2 mol % (*R*)-**1g** and 2.0 equiv **3a**.

or $Rh_2(TPA)_4$, reduced the enantioselectivity to 10% and 16% ee, respectively (entries 9 and 10). Remarkably, the use of $Rh_2(TFA)_4$, a strong Lewis acid, improved the enantioselectivity to 92% ee (entry 11). When the reaction temperature was increased to 45 °C, the enantioselectivity increased to 95% ee (entry 12). Further heating the reaction to reflux, the desired arylation product was obtained with retained enantioselectivity but lower yield (entry 13). However, the reaction performed at 0 °C became sluggish with significantly lowered yield and enantioselectivity (entry 14). The yield and enantioselectivity were further increased to 79% and 97% ee, respectively, when 2 mol % catalyst (*R*)-**1g** and 2.0 equiv of substrate **3a** were used (entry 15). Note that the arylation reaction occurred specifically at the *para* position of the 1-phenylpyrrolidine. The reaction is sensitive to water, and the addition of water into the reaction mixture leads to the decrease of yield and enantioseletivity (Table S1).

Using the optimal reaction conditions, we evaluated the reactions of various α-aryl-α-diazoacetates **2** with 1-phenylpyrrolidine (**3a**) (Table 2). Substituents at the *para* and *meta* positions of the aryl ring of the α-aryl-α-diazoacetates had a negligible impact on the yield and enantioselectivity of the reaction; substrates with this type of substitution underwent arylation in 30 min and afforded the corresponding chiral α-diarylacetates (**4a**–**4i** and **4k**) in good yields (66–95%) with excellent enantioselectivities (93–97% ee). Diazoacetate **2j**, which has an *ortho* fluoro substituent, gave a relatively low yield (54%). Diazoacetates with a fused ring, such as benzo[*d*][1,3]-dioxol-5-yl (**2l**) and 2-naphthyl (**2m**), were also suitable substrates for the reaction and afforded the corresponding products (**4l** and **4m**) in satisfactory yields and enantioselectivities. The phenyldiazoacetates with bulkier ester moieties

Table 2. Enantioselective Arylation of α-Aryl-α-diazoacetates with 1-Phenylpyrrolidine[a]



[a]The reaction conditions and analysis method were the same as those described in Table 1, entry 15.

exhibited lower yields and enantioselectivities (**4n** and **4o**). Arylation product **4i** was determined to have the (*R*)-configuration by means of X-ray diffraction analysis of a single crystal (Figure 2).

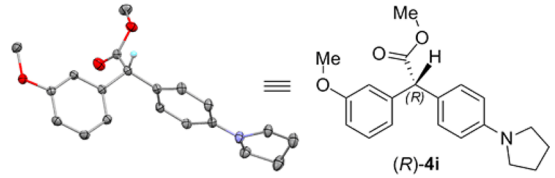


Figure 2. X-ray structure of (*R*)-**4i**. H atoms, except the one at the chiral center, have been omitted for clarity.

We also investigated the arylation reactions of various aniline derivatives with diazoacetate **2a** (Table 3). The electronic properties of *meta* substituents on the aryl ring of the 1-arylpyrrolidines had a negligible effect on the enantioselectivity (**4p**–**4r**). In contrast, the effects of *ortho* substituents differed depending on their steric and electronic characteristics: relatively small electron-withdrawing groups such as Br or F gave excellent enantioselectivities (**4t**, 94% ee; **4u**, 91% ee), whereas relatively bulky groups and the electron-donating methyl group afforded low enantioselectivity (**4s**, 58% ee). Like the 1-arylpyrrolidines, 4-phenylmorpholine also underwent the arylation reaction, producing corresponding product **4v** in good yield (81%) with excellent enantioselectivity (97% ee). 1-Phenylpiperidine and *N*,*N*-dimethylaniline reacted with **2a** to afford arylation products in good yields, but the enantioselectivities were only moderate (**4w**, 64% ee; **4x**, 59% ee). When other benzene derivatives, such as anisole and toluene, were tested in the reaction with **2a**, only carbene dimerization products were obtained.

This arylation reaction could easily be scaled up to a 1 g scale without reduction of the yield or enantioselectivity; the reaction of **2m** (1.13 g) and **3a** afforded **4m** in 78% yield with 94% ee

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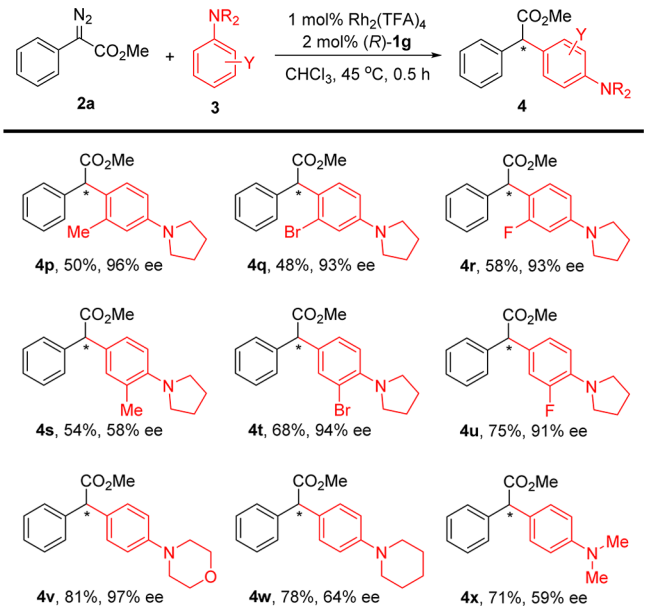
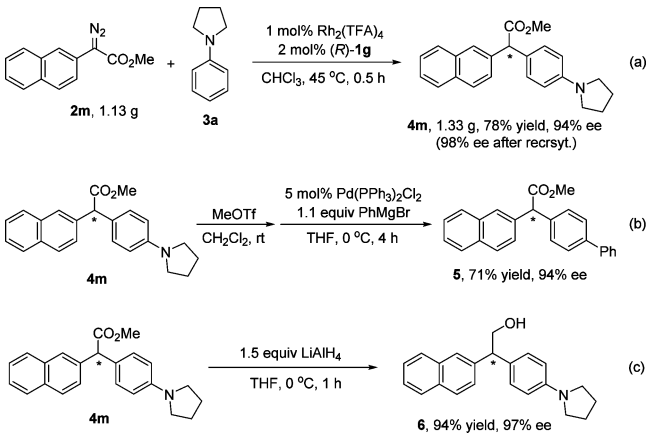
Table 3. Enantioselective Arylation of Methyl 2-Phenyl-2-diazoacetate with Aniline Derivatives[a]



[a]The reaction conditions and analysis method were the same as those described in Table 1, entry 15.

(Scheme 2a). The amino and carboxylic groups of the arylation products could serve as handles for various transformations.[8] For

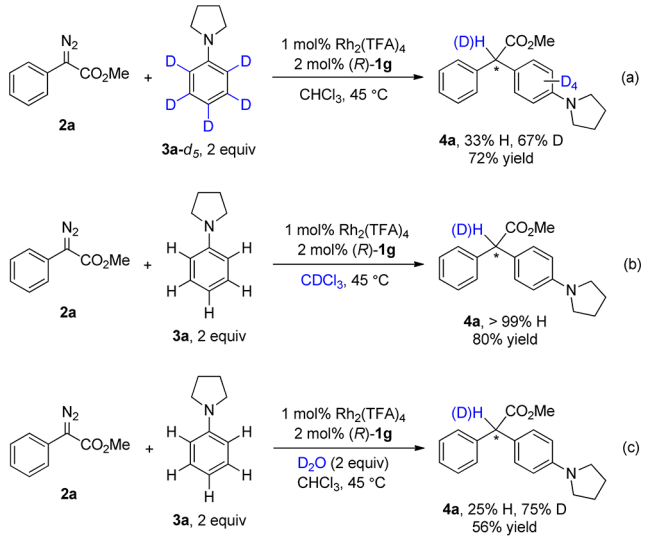
Scheme 2. Applications of the Chiral α-Diarylacetates



example, the pyrrolidinyl group of **4m** was converted to a phenyl group by means of a palladium-catalyzed cross coupling with a Grignard reagent in the presence of methyl trifluoromethanesulfonate (Scheme 2b).[8e] Reduction of the ester group of **4m** produced chiral β-diaryl alcohol **6** (Scheme 2c), a structural unit found in many bioactive compounds.[9]

To investigate the mechanism of the arylation reaction, we performed deuterium-labeling experiments. When 1-(pentadeuterophenyl)pyrrolidine **3a** was used, arylation product **4a** was obtained with 67% deuterium incorporation at the chiral center (Scheme 3a). This result indicates that the hydrogen atom on the chiral center was not derived exclusively from the *para* position of **3a**-d_5. The reaction performed in $CDCl_3$ gave a product without deuterium, which rules out the possibility that the hydrogen atom came from the solvent (Scheme 3b). The addition of a stoichiometric amount of deuterium oxide to the

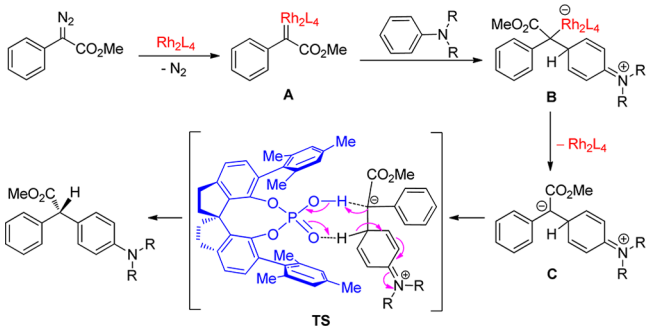
Scheme 3. Deuterium-Labeling Experiments



system resulted in the formation of an arylation product with 75% deuterium incorporation at the chiral center, indicating that the hydrogen atom could be derived partly from water present in the reaction medium (Scheme 3c). Taken together, the results of these experiments support a stepwise mechanism.[10]

On the basis of the deuterium-labeling experiments and previous studies reported by Davies[4] and Hu,[11] we propose the following mechanism (Scheme 4): First, Rh carbene **A** generated

Scheme 4. Proposed Mechanism and Chiral Induction Model



from the α-aryl α-diazoacetate reacts with the electron-rich aromatic ring of the aniline to form zwitterion **B**. Dissociation of rhodium from **B** generates metal-free zwitterion **C**, which undergoes a 1,2-proton shift to give the arylation product. The 1,2-proton shift is mediated by the SPA and occurs via a proton shuttle model (**TS**), and it is at this step that the chiral induction occurs.[12] Water present in trace amounts in the reaction medium may exchange a proton with intermediate **B** or **C** and may even be present in the transition state (**TS**) as a bridge, which could explain the deuterium distribution observed in the reactions shown in Scheme 3a,c. Investigation of the details of the reaction mechanism is underway in our laboratory.

In conclusion, asymmetric arylation reaction of α-aryl-α-diazoacetates with aniline derivatives was achieved with an achiral dirhodium complex and a chiral SPA as cocatalysts. The reaction provides a new approach to the synthesis of chiral α-diarylacetates in good yields with high enantioselectivities. Our results demonstrate that chiral proton shuttle catalysts can be used for otherwise difficult to accomplish transition-metal-

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catalyzed asymmetric reactions in which chiral induction occurs at the proton shift step.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental and characterization data, including ^{1}H and ^{13}C NMR spectra for all the new compounds, chiral HPLC spectra for the products, and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05086.

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Notes

The authors declare no competing financial interest.

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