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Highly Enantioselective Synthesis of *N,N*-Dialkylbenzamides with Aryl–Carbonyl Axial Chirality by Rhodium-Catalyzed [2+2+2] Cycloaddition

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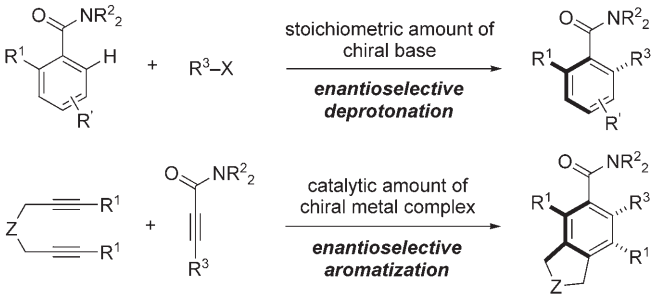
2,6-Disubstituted *N,N*-dialkylbenzamides are known to exist as atropisomers due to the high rotational barrier around the aryl–carbonyl single bond.[1] Their interesting atropisomerism[1] and considerable utility as chiral reagents[2] have prompted organic chemists to explore their asymmetric synthesis.[3–7] Kinetic resolution by Sharpless dihydroxylation,[3] and dynamic kinetic resolution of racemic 2-formylnaphthamides by the reaction with a chiral diamine or an amino alcohol[4] and the proline-catalyzed aldol reaction[5] have been employed as resolution methods. The stereoselective alkylation of an enantiopure planar chiral (2-methyl-*N,N*-diethylbenzamide)chromium complex was reported as a diastereoselective method,[6] and the enantioselective deprotonation of a (2,6-dimethyl-*N,N*-diethylbenzamide)chromium complex[6] and *N,N*-dialkyl-1-naphthamides (Scheme 1)[7] with a stoichiometric amount of chiral lithium amide followed by alkylation has been used as an enantioselective method. However, the straightforward catalytic enantioselective method has not been realized to date. Furthermore, *N,N*-dialkylbenzamides bearing a sterically demanding *ortho* substituent, which possess highly stable axial chirality, are difficult to prepare by existing methods. Recently, we reported the enantioselective synthesis of axially chiral compounds by cationic rhodium(I)/modified-binap-catalyzed [2+2+2] cycloadditions.[8,9] Herein, we report the first catalytic enantioselective construction of the aryl–carbonyl axial chirality of *N,N*-dialkylbenzamides in high yields



Scheme 1. Enantioselective synthesis of *N,N*-dialkylbenzamides with aryl–carbonyl axial chirality.

with outstanding enantiomeric excesses (>99% *ee*) by aromatization through a cationic rhodium(I)/segphos- or binap-catalyzed [2+2+2] cycloaddition of 1,6-diynes with *N,N*-dialkylalkynylamides (Scheme 1).

We first investigated a rhodium-catalyzed [2+2+2] cycloaddition of malonate-derived 1,6-diyne **1a** with *N,N*-diisopropylalkynylamide **2a** bearing a sterically demanding 2-methoxypropyl group at an alkyne terminus by employing various axially chiral biarylbisphosphine ligands (Table 1). We were pleased to find that the reactions proceeded to give the desired axially chiral benzamide (−)-**3aa** with excellent *ee*, and high yield of **3aa** was achieved by using binap or segphos as a ligand (Table 1, entries 1 and 4). When a solution of **1a** in CH_2Cl_2 was added to a solution of **2a** and Rh catalyst in CH_2Cl_2, the yields of **3aa** were improved further (Table 1, entries 5 and 6).

Thus, the scope of this cycloaddition was examined with respect to *N,N*-dialkylalkynylamides (Table 2, entries 1–7). Not only sterically demanding diisopropylamide (**2a**, Table 2, entry 1) but also diethylamide (**2b**, Table 2, entry 2), dimethylamide (**2c**, Table 2, entry 3), and 1-piperidinylamide (**2d**, Table 2, entry 4) furnished the corresponding benzamides with stable axial chirality in high yields with excellent *ee* values. Furthermore, the reactions of not only 2-methoxypropyl (**2a**) but also tertiary (**2e**, Table 2, entry 5),[10] secondary (**2f**, Table 2, entry 6), and primary (**2g**, Table 2, entry 7) alkyl-substituted alkynylamides gave

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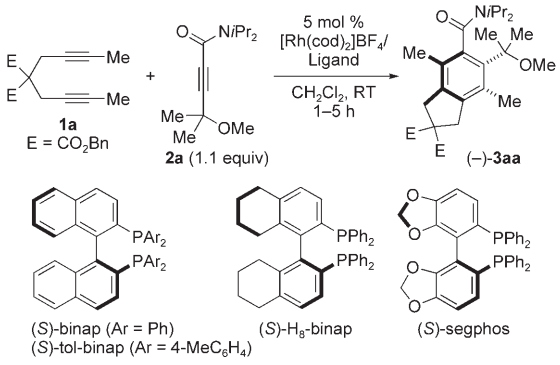
Table 1. Screening of ligands for Rh-catalyzed enantioselective synthesis of axially chiral *N*,*N*-dialkylbenzamide **3aa**.[a]

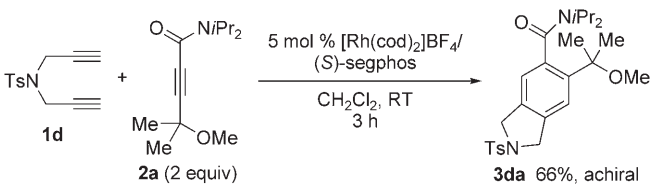


Entry	Ligand	Time [h]	Yield [%][b]	*ee* [%]
1	(*S*)-binap	1	80	>99
2	(*S*)-tol-binap	5	70	>99
3	(*S*)-H_8-binap	1	59	98
4	(*S*)-segphos	1	82	>99
5[c]	(*S*)-binap	1	84	>99
6[c]	(*S*)-segphos	3	90	>99

[a] $[Rh(cod)_2]BF_4$ (0.0050 mmol), ligand (0.0050 mmol), **1a** (0.10 mmol), **2a** (0.11 mmol, 1.1 equiv), and CH_2Cl_2 (1.5 mL) were used. A solution of **1a** and **2a** was added to a solution of Rh catalyst. [b] Yield of isolated product. [c] A solution of **1a** was added to a solution of **2a** and Rh catalyst.

the corresponding benzamides with stable axial chirality in high yields with excellent *ee* values. In the case of the alkynylamides **2a**-**e** bearing tertiary substituents at an alkyne terminus, segphos is a suitable ligand (Table 2, entries 1–5). On the other hand, binap is a suitable ligand for the alkynylamides **2f** and **2g** bearing a secondary or primary substituent at an alkyne terminus (Table 2, entries 6 and 7).

The generality of this cycloaddition was subsequently examined with respect to 1,6-diynes. Thus, tosylamide- (**1b**, Table 2, entry 8) and ether-linked (**1c**, Table 2, entry 9)[10] 1,6-diynes could participate in this reaction to give the corresponding axially chiral benzamides in high yields with excellent *ee* values. The methyl group at the *ortho* position of *N*,*N*-dialkylbenzamides is necessary to construct the stable axial chirality. Although the reaction of terminal 1,6-diyne **1d** with **2a** furnished the corresponding benzamide **3da** in good yield, **3da** does not possess stable axial chirality at room temperature despite of the sterically demanding substituents on the nitrogen atom and at the *ortho* position (Scheme 2).[11]



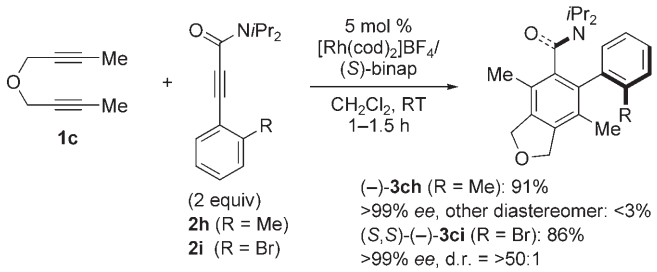
Scheme 2. Rh^{I+}/segphos-catalyzed reaction of terminal 1,6-diyne **1d** with monoyne **2a**.

Table 2. Rh^{I+}/segphos- or binap-catalyzed enantioselective synthesis of axially chiral *N*,*N*-dialkylbenzamides **3**.[a]

Entry	Diyne **1**	Monoyne **2**	Product **3**/ Yield [%][b], *ee* [%]
1	**1a** (E = CO_2Bn)	**2a** (R = *i*Pr)	(–)-**3aa** 92, >99
2	**1a** (E = CO_2Bn)	**2b** (R = Et)	(–)-**3ab** 94, >99
3	**1a** (E = CO_2Bn)	**2c** (R = Me)	(+)-**3ac** 90, >99
4	**1a** (E = CO_2Bn)	**2d**	(–)-**3ad** 98, >99
5[c]	**1a** (E = CO_2Bn)	**2e**	(–)-**3ae** 90, >99
6[d]	**1a** (E = CO_2Bn)	**2f**	(+)-**3af** >99, >99
7[d]	**1a** (E = CO_2Bn)	**2g**	(+)-**3ag** 96, >99
8[e]	**1b** (Z = NTs)	**2a**	(–)-**3ba** 85, >99
9[c]	**1c** (Z = O)	**2a**	(–)-**3ca** 81, >99

[a] Reactions were conducted by using $[Rh(cod)_2]BF_4$ (0.0075 mmol), (*S*)-segphos (0.0075 mmol), **1** (0.15 mmol), **2** (0.165 mmol, 1.1 equiv), and CH_2Cl_2 (2.0 mL) at room temperature for 1 h. [b] Yield of isolated product. [c] **2**: 2 equiv. [d] Ligand: (*S*)-binap. [e] CH_2Cl_2: 1.5 mL.

Next, the reaction of a *N*,*N*-dialkylalkynylamide bearing a 2-substituted phenyl group at an alkyne terminus with a 1,6-diyne was examined, which would construct both aryl–carbonyl and aryl–aryl axial chiralities in a single step (Scheme 3).[12] We were pleased to find that alkynylamide **2h** bearing a *o*-tolyl group at an alkyne terminus reacted with 1,6-diyne **1c** in the presence of the Rh^{I+}/(*S*)-binap catalyst to give the corresponding axially chiral biarylbenzamide (–)-**3ch** in high yield with excellent enantio- and diastereoselectivity.[10] Similarly, the reaction of 2-bromo-substituted alkynylamide **2i** also provided the corresponding axially



Scheme 3. Rh^{I}+/binap-catalyzed construction of both aryl–carbonyl and aryl–aryl axial chiralities.

chiral biarylbenzamide (−)-**3ci** with excellent enantio- and diastereoselectivity.[10] The absolute configuration of (−)-**3ci** was determined to be (*S,S*) by the anomalous dispersion method (Figure 1).[13]

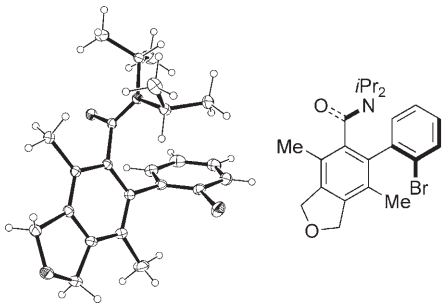


Figure 1. ORTEP drawings of (*S,S*)-(−)-**3ci** drawn at the 50% probability level.

Finally, the rate of racemization of these new axially chiral *N,N*-dialkylbenzamides was investigated at 80°C in $(CH_2Cl)_2$ (Table 3).[14,15] The effect of the substituents on the nitrogen center was examined, which revealed that the rates of racemization of *N,N*-dimethylamide (**3ac**, Table 3, entry 3) and 1-piperidinylamide (**3ad**, Table 3, entry 4) are higher than those of *N,N*-diisopropylamide (**3aa**, Table 3, entry 1) and *N,N*-diethylamide (**3ab**, Table 3, entry 2). The effect of the *ortho* substituents was also examined, which revealed that *ortho*-(2-methoxypropyl)benzamide (**3aa**, Table 3, entry 1) and *ortho*-(*tert*-butyl)benzamide (**3ae**, Table 3, entry 5) possess highly stable axial chirality, whereas *ortho*-(isopropyl)benzamide (**3af**, Table 3, entry 6) was gradually racemized and *ortho*-(*n*-butyl)benzamide (**3ag**, Table 3, entry 7) was completely racemized after 24 h. Thus, the substituents on the nitrogen center and at the *ortho* position of *N,N*-dialkylbenzamides significantly affect the thermal stability of axially chirality.

Table 3. Rate of racemization of axially chiral *N,N*-dialkylbenzamides **3** [$(CH_2Cl)_2$, 80°C].

Entry	**3**	*ee* [%]			
		0 h	1 h	6 h	24 h
1	**3aa**	>99	>99	98	95
2	**3ab**	>99	>99	98	93
3	**3ac**	>99	98	93	77
4	**3ad**	>99	98	89	70
5	**3ae**	>99	>99	>99	97
6	**3af**	>99	97	91	73
7	**3ag**	97[a]	76	11	0

[a] Slight racemization of this compound was observed on storage for several weeks.

In conclusion, we have developed the first catalytic enantioselective synthesis of axially chiral *N,N*-dialkylbenzamides in high yields with outstanding *ee* values (>99% *ee*) by a cationic rhodium(I)/segphos- or binap-catalyzed [2+2+2] cycloaddition of 1,6-diynes with *N,N*-dialkylalkynylamides. Furthermore, the use of *N,N*-dialkylalkynylamides bearing a 2-substituted phenyl group at an alkyne terminus successfully constructed both aryl–carbonyl and aryl–aryl axial chiralities with excellent enantio- and diastereoselectivity. Utilization of these new axially chiral *N,N*-dialkylbenzamides for chiral reagents is currently underway in our laboratory.

Experimental Section

Typical procedure for Rh-catalyzed [2+2+2] cycloaddition (Table 2, entry 1): A solution of (*S*)-segphos (4.6 mg, 0.0075 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of $[Rh(cod)_2]BF_4$ (3.0 mg, 0.0075 mmol) in CH_2Cl_2 (0.5 mL) at room temperature, and the mixture was stirred for 5 min. The resulting solution was stirred under H_2 (1 atm) at room temperature for 1 h, concentrated to dryness, and dissolved in CH_2Cl_2 (0.5 mL). To this solution was added a solution of **2a** (37.2 mg, 0.165 mmol) in CH_2Cl_2 (0.5 mL). Then a solution of **1a** (58.3 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over 5 min at room temperature. The solution was stirred at room temperature for 1 h. The resulting solution was concentrated and purified by silica gel chromatography (hexane/EtOAc = 5:1–2:1), which furnished (−)-**3aa** (85.1 mg, 0.139 mmol, 92% yield, >99% *ee*) as a pale yellow oil.

Acknowledgements

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Keywords: axial chirality · benzamides · cycloaddition · enantioselective catalysis · rhodium

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