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Iron-Catalyzed C–H Fuctionalization of Indoles

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Abstract: An easily available iron catalyst was developed to accomplish the C–H functionalization of indoles with α-aryl-α-diazoesters in high yields under mild conditions. The asymmetric C–H functionalization of indoles was also realized by using iron complexes of chiral spiro bisoxazolines with up to 78% *ee*.

Keywords: C–H functionalization; chiral spiro ligands; indoles; iron

Transition metal-catalyzed C–H functionalization by diazo compounds represents one of the most efficient C–H bond activation approaches.[1] Thanks to the development of chiral dirhodium(II) catalysts, asymmetric C–H functionalization of a variety of sp^3 hybrid C–H bonds by metal carbenes derived from diazo compounds has become a reliable and widely applied method in organic synthesis nowadays.[2] Although the sp^2 hybrid C–H functionalization has been extensively investigated,[1a] only a few asymmetric sp^2 C–H functionalization reactions were documented. In 1995, Hashimoto et al.[3] reported an intramolecular asymmetric phenyl ring C–H functionalization *via* desymmetrization by using the catalyst [Rh_2(*S*-PTTL)$_4$] [rhodium(II) *N*-phthaloyl-(*S*)-*tert*-leucinate] with 88–98% *ee*. Schmaltz[4] and Merlic[5] utilized copper- and rhodium-catalyzed asymmetric sp^2 C–H functionalization reactions to prepare planar-chiral ferrocenes and (η^6-arene)tricarbonylchromium complexes in good enantioselectivities (78% and 90% *ee*, respectively).

Since the indole ring is probably the most ubiquitous heterocycle in nature, the development of approaches for the functionalization of indoles has attracted extensive attention recently.[6] Transition metal-catalyzed C–H functionalization of indoles provides one of the most efficient methods for the synthesis of indole derivatives. Although several catalysts including rhodium, copper, and ruthenium have been developed for the C–H functionalization of indoles in the past decades,[7] only quite recently was a highly enantioselective C–H functionalization of indoles disclosed by Fox and co-workers.[8] With catalytic amounts of [Rh_2(*S*-NTTL)$_4$] {dirhodium(II) tetrakis[*N*-(1,8-naphthaloyl)-(*S*)-*tert*-leucinate]}, the α-alkyl-α-diazoesters reacted with indoles at C-3 to produce α-alkyl-α-indolylacetates in high yields and high enantioselectivities (79–99% *ee*). From a synthetic point of view, the indole functionalization with α-aryl-α-diazoesters is a very useful reaction for the construction of α-aryl-α-indolylacetates, which are key intermediates for the synthesis of a wide range of bioactive compounds. For instance, Pfizer's chiral endothelin antagonists UK-350,926 and UK-350,862 (Figure 1) can be easily prepared *via* indole functionalization with the corresponding α-aryl-α-diazoesters.[9] However, when Davies et al.[10] tried the C–H functionalization of 1,2-dimethylindole with methyl α-phenyl-α-diazoacetate by using the catalyst [Rh_2(*S*-DOSP)$_4$] [rhodium(II) (*S*)-*N*-(dodecyl-benzenesulfonyl)prolinate], only negligible enantioselectivity (<5% *ee*) was obtained. Therefore, efficient chiral catalysts for C–H functionalization of indoles with α-aryl-α-diazoesters are still highly desired.

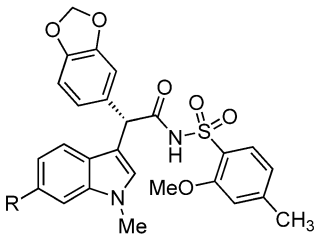
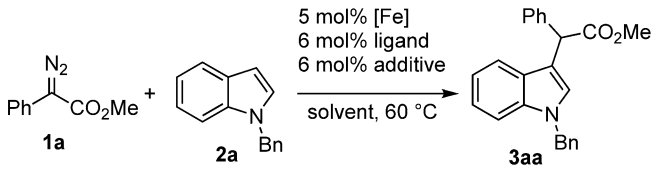


Figure 1. Chiral endothelin antagonists UK-350,926 and UK-350,862.

Table 1. Iron-catalyzed C–H functionalization of *N*-benzylindole with α-diazo-α-phenylacetate.[a]



Entry	[Fe]	Ligand	Solvent	Time [h]	Yield [%][b]
1	$FeCl_2$	none	DCE	30	10
2	$FeCl_3$	none	DCE	30	5
3	$Fe(acac)_2$	none	DCE	30	NR[c]
4	$Fe(OAc)_2$	none	DCE	30	45
5	$Fe(ClO_4)_3$	none	DCE	6	50
6	$Fe(BF_4)_2$	none	DCE	4	54
7	$Fe(ClO_4)_2$	none	DCE	4	60
8[d]	$Fe(ClO_4)_2$	none	DCE	3	72
9[d]	$Fe(ClO_4)_2$	TMEDA	DCE	3	96
10[d]	$Fe(ClO_4)_2$	TMEDA	$CHCl_3$	4	92
11[d]	$Fe(ClO_4)_2$	TMEDA	toluene	4	90
12[d]	$Fe(ClO_4)_2$	TMEDA	THF	48	15
13[d]	$Fe(ClO_4)_2$	TMEDA	CH_3CN	48	10
14[d,e]	$Fe(ClO_4)_2$	TMEDA	DCE	10	96
15[d,f]	$Fe(ClO_4)_2$	TMEDA	DCE	5	93

[a] *Reaction conditions:* [Fe]/ligand/**1a**/**2a** = 0.015/0.018/0.36/0.3 (mmol), in 5 mL of solvent at 60 °C.
[b] Isolated yield.
[c] No reaction.
[d] 6 mol% $NaBAr_F$ was added.
[e] The reaction was performed at 25 °C.
[f] Using 1 mol% of catalyst.

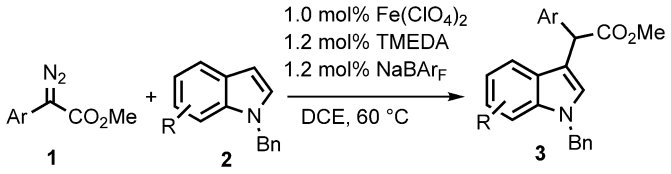
As part of our continuing efforts on transition metal-catalyzed carbene transformations,[11] we herein report an iron-catalyzed C–H functionalization of indoles with α-aryl-α-diazoesters. An easily available iron catalyst was developed to accomplish the C–H functionalization of indoles in high yields. The asymmetric C–H functionalization of indoles was also realized by using iron complexes of chiral spiro bisoxazolines with up to 78% *ee*.

In the initial studies, the reaction of 1-benzylindole (**2a**) with methyl α-diazophenylacetate (**1a**) was performed in 1,2-dichloroethane (DCE) at 60 °C in the presence of 5 mol% iron catalyst. Firstly, various iron catalysts were evaluated (Table 1). Except for $Fe(acac)_2$, all the tested Fe(II) and Fe(III) salts promoted the reaction to give the desired product, methyl 2-(1-benzylindol-3-yl)-2-phenylacetate (**3aa**), in low to moderate yields (Table 1, entries 1–7). The ionic catalysts $Fe(OAc)_2$, $Fe(BF_4)_2$ and $Fe(ClO_4)_2$ afforded higher yields (entries 5–7). With $Fe(ClO_4)_2$ as catalyst precursor, the addition of $NaBAr_F$ {sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate}, which provided a bulky and non-coordinating anion, slightly improved the reaction rate and yield (entry 8). To our delight, when *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was introduced as a ligand, the yield of the reaction significantly increased to 96% (entry 9). Besides DCE, $CHCl_3$ and toluene were also suitable solvents for the reaction in terms of reaction rate and yield (entries 10 and 11). On the contrary, the coordinating solvents THF and CH_3CN dramatically slowed down the reaction and gave very low yields (entries 12 and 13). The reaction can also be performed at room temperature albeit a slightly longer reaction time was needed (entry 14). The catalyst $Fe(ClO_4)_2$/TMEDA showed high activity, with 1 mol% being sufficient for achieving high yield (entry 15). This result demonstrates that the iron catalyst is comparable with rhodium and copper catalysts for the C–H functionalization of indoles.[7]

Under the optimal reaction conditions, various α-aryl-α-diazoacetates were examined in the C–H functionalization of 1-benzylindole (**2a**). All tested α-aryl-α-diazoacetates with different substituents on the phenyl ring gave the desired products in high to excellent yields (85–95%) (Table 2, entries 2–10). Diazo compounds **1h** and **1i** with a 2-substituted phenyl group required a higher catalyst loading for obtaining satisfactory yields (entries 8 and 9). Additionally, methyl α-naphthyl-α-diazoacetate (**1k**) exhibited a similar reactivity to that of **1a**, affording the corresponding product in 92% yield (entry 11). The substituent effect on the indole ring was then investigated. An electron-withdrawing group at the 5-position of indole had a negligible effect on the reaction and the corresponding products were isolated in high yields (entries 12–14). On the contrary, an electron-donating group at C-2, C-3, C-4, and C-5 of the indole significantly reduced the reaction rate and yield, and a higher reaction temperature was required for full conversion (entries 15–18). For 3-methyl-substituted indole **2g**, the C–H functionalization took place at C-2 of the indole ring to give the corresponding product in 72% yield (entry 17). Besides the α-aryl-α-diazoacetates, α-diazopropionate and α-diazoacetate, which contain α-methyl and α-H moieties, respectively, were also studied. Both of them underwent the C–H functionalization under standard reaction conditions, however, the competitive carbene dimerization reaction became significant and the yields for desired products were only moderate (42% and 36%, respectively).

The asymmetric version of the iron-catalyzed C–H functionalization of indoles was then tried. We first investigated chiral spirobisoxazoline ligands (Table 3, entries 1–5), which proved to be one of the best chiral ligands for asymmetric heteroatom-hydrogen bond insertion reactions.[11] We were delighted to find that the ligand (*R*$_a$,*S*,*S*)-**4a** containing phenyl groups on the oxazoline rings afforded the C–H functionalization product in high yield (90%) with moderate enantioselectivity (61% *ee*) in the reaction of **1a** with indole **2a**

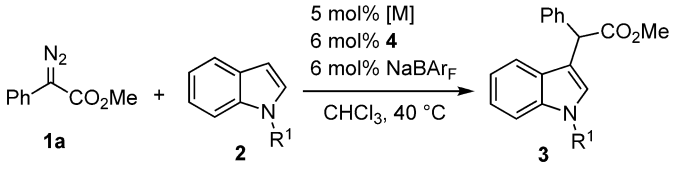
Table 2. Iron-catalyzed C–H functionalization of indoles with α-aryl-α-diazoesters.[a]

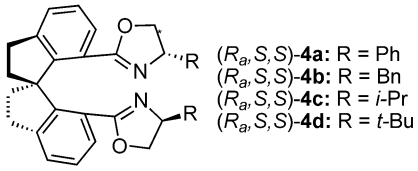


Entry	Ar (**1**)	R (**2**)	**3**	Time [h]	Yield [%]
1	C_6H_5 (**1a**)	H (**2a**)	**3aa**	5	93
2	4-Br-C_6H_4 (**1b**)	H (**2a**)	**3ba**	5	95
3	4-Me-C_6H_4 (**1c**)	H (**2a**)	**3ca**	4	95
4	4-MeO-C_6H_4 (**1d**)	H (**2a**)	**3da**	2	93
5	3-Br-C_6H_4 (**1e**)	H (**2a**)	**3ea**	7	90
6	3-Me-C_6H_4 (**1f**)	H (**2a**)	**3fa**	6	93
7	3-MeO-C_6H_4 (**1g**)	H (**2a**)	**3ga**	5	93
8[b]	2-Cl-C_6H_4 (**1h**)	H (**2a**)	**3ha**	5	92
9[b,c]	2-Me-C_6H_4 (**1i**)	H (**2a**)	**3ia**	6	85
10	3,4-$(MeO)_2C_6H_3$ (**1j**)	H (**2a**)	**3ja**	1	88
11	2-naphthyl (**1k**)	H (**2a**)	**3ka**	6	92
12	C_6H_5 (**1a**)	5-F (**2b**)	**3ab**	4	91
13	C_6H_5 (**1a**)	5-Cl (**2c**)	**3ac**	4	93
14	C_6H_5 (**1a**)	5-Br (**2d**)	**3ad**	5	91
15[d]	C_6H_5 (**1a**)	5-Me (**2e**)	**3ae**	15	85
16[d]	C_6H_5 (**1a**)	4-BnO (**2f**)	**3af**	18	74
17[d,e]	C_6H_5 (**1a**)	3-Me (**2g**)	**3ag**	12	72
18[d]	C_6H_5 (**1a**)	2-Me (**2h**)	**3ah**	14	82

[a] *Reaction conditions and analysis:* the same as those of Table 1, entry 15.
[b] 5 mol% of catalyst was used.
[c] The reaction was performed at 40 °C.
[d] The reaction was performed at 80 °C.
[e] The reaction took place at C-2 of indole.

Table 3. Iron-catalyzed asymmetric C–H functionalization of indoles: optimization of reaction conditions.[a]

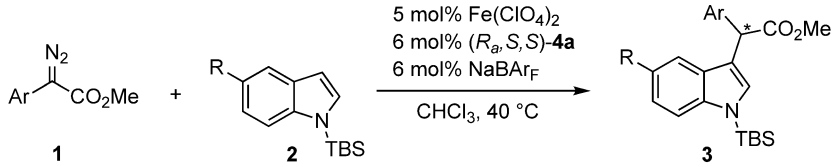




Entry	Ligand	[M]	R^1	Time [h]	Yield [%][b]	*ee* [%][c]
1	(S_a,*S*,*S*)-**4a**	$Fe(ClO_4)_2$	Bn (**2a**)	15	50	−26
2	(R_a,*S*,*S*)-**4a**	$Fe(ClO_4)_2$	Bn (**2a**)	18	90	61
3	(R_a,*S*,*S*)-**4b**	$Fe(ClO_4)_2$	Bn (**2a**)	35	70	16
4	(R_a,*S*,*S*)-**4c**	$Fe(ClO_4)_2$	Bn (**2a**)	48	24	12
5	(R_a,*S*,*S*)-**4d**	$Fe(ClO_4)_2$	Bn (**2a**)	48	NR[d]	–
6	(R_a,*S*,*S*)-**4a**	CuCl	Bn (**2a**)	1	70	41
7	(R_a,*S*,*S*)-**4a**	AgOTf	Bn (**2a**)	20	74	29
8	(R_a,*S*,*S*)-**4a**	AuCl	Bn (**2a**)	48	24	49
9	(R_a,*S*,*S*)-**4a**	$CoCl_2$	Bn (**2a**)	20	49	27
10	(R_a,*S*,*S*)-**4a**	$Fe(ClO_4)_2$	Me (**2i**)	30	90	60
11	(R_a,*S*,*S*)-**4a**	$Fe(ClO_4)_2$	TBS (**2j**)[e]	8	92	73

[a] *Reaction conditions:* [M]/**4**/$NaBAr_F$/**1a**/**2** = 0.015/0.018/0.018/0.3/0.3 (mmol), in 5 mL $CHCl_3$ at 40 °C.
[b] Isolated yield.
[c] Determined by SFC using a chiral column.
[d] No reaction.
[e] TBS = *tert*-butyldimethylsilyl.

Table 4. Iron-catalyzed asymmetric C–H functionalization of indoles with α-aryl-α-diazoesters.[a]



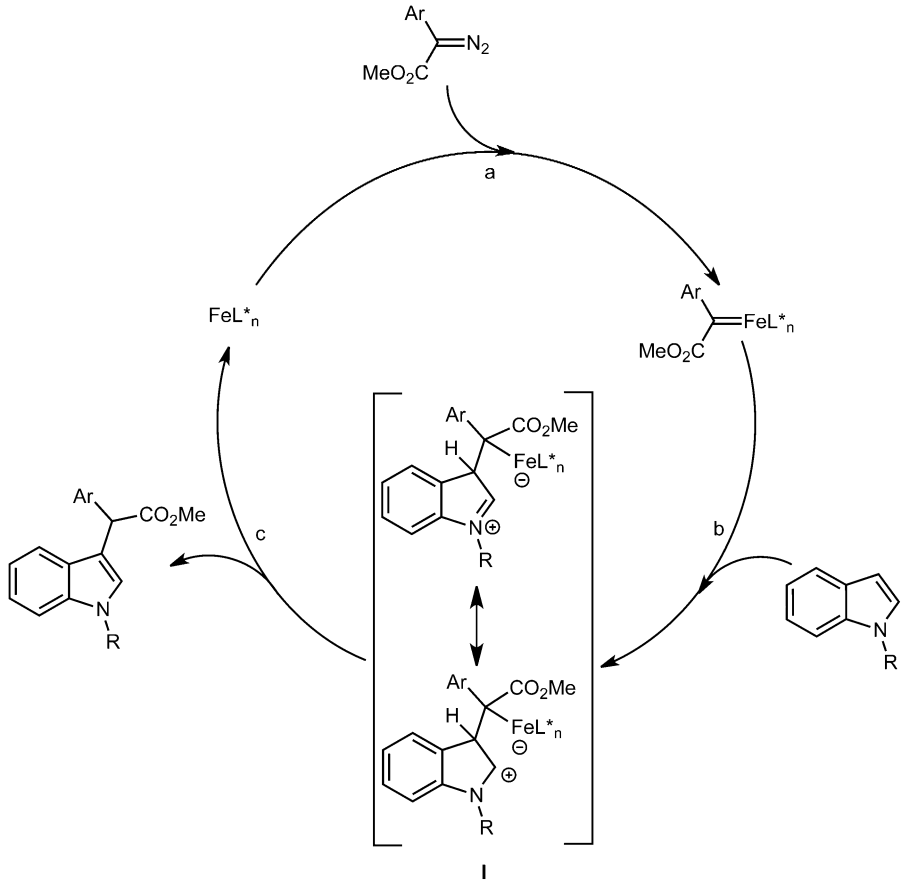
Entry	Ar (**1**)	R (**2**)	**3**	Time [h]	Yield [%]	*ee* [%]
1	C_6H_5 (**1a**)	H (**2j**)	**3aj**	8	92	73
2	4-Cl-C_6H_4 (**1l**)	H (**2j**)	**3lj**	4	89	71
3	4-Br-C_6H_4 (**1b**)	H (**2j**)	**3bj**	4	86	65
4	4-Me-C_6H_4 (**1c**)	H (**2j**)	**3cj**	8	86	63
5	3-F-C_6H_4 (**1m**)	H (**2j**)	**3mj**	8	86	67
6	3-Cl-C_6H_4 (**1n**)	H (**2j**)	**3nj**	4	88	71
7	3-Br-C_6H_4 (**1e**)	H (**2j**)	**3ej**	3	92	78
8	3-CF_3-C_6H_4 (**1o**)	H (**2j**)	**3oj**	4	90	76
9	3-MeO-C_6H_4 (**1g**)	H (**2j**)	**3gj**	24	76	60
10	2-Me-C_6H_4 (**1i**)	H (**2j**)	**3ij**	30	60	39
11	3,4-$Cl_2C_6H_3$ (**1p**)	H (**2j**)	**3pj**	10	86	72
12	2-naphthyl (**1k**)	H (**2j**)	**3kj**	24	70	65
13	C_6H_5 (**1a**)	Cl (**2k**)	**3ak**	6	80	73
14	C_6H_5 (**1a**)	Me (**2l**)	**3al**	8	94	60

[a] *Reaction conditions and analysis:* the same as those of Table 3, entry 11.

(entry 2). When the reaction was performed on a double scale (0.6 mmol), the same levels of reactivity and enantioselectivity (18 h, 91%, 61% *ee*) were observed. No epimerization of the product **3aa** was observed after stirring for 12 hour under the reaction conditions, indicating that the stereochemistry of the C–H functionalization products of indoles is stable under the reaction conditions. Other chiral bisoxazoline ligands such as BOX and Pybox were less efficient in this C–H functionalization reaction.[12] Other transition metals including copper, silver, gold, and cobalt were also evaluated and lower enantioselectivies were obtained (entries 6–9). The N-protecting group of indole strongly affected the enantioselectivity of the reaction, with *N*-TBS (*tert*-butyldimethylsilyl)-indole (**2j**) giving the best result (entry 11).

The substrate scope of the reaction was studied. For all tested α-aryl-α-diazoacetates with *para*- or *meta*-substituted phenyl ring, high yields (76–92%) and moderate to good enantioselectivities (60–78% *ee*) were obtained (Table 4, entries 2–9). The diazoesters with an electron-withdrawing group on the phenyl ring gave higher enantioselectivity, with methyl α-(3-bromophenyl)-α-diazoacetate (**1e**) showing the highest enantioselectivity (78% *ee*) (entry 7). The reaction was quite sensitive to the steric hindrance of the substrate. The substitution at the *ortho*-position of the phenyl ring of the substrate dramatically slowed down the reaction and provided a low yield and low enantioselectivity. For example, the reaction of methyl α-(2-methylphenyl)-α-diazoacetate (**1i**) afforded the product **3ij** in only 60% yield with 39% *ee* (entry 10). However, the reaction of methyl α-(2-chlorophenyl)-α-diazoacetate (**1h**) yielded a racemic product in 76% yield. The indoles with 5-Cl (**2k**) and 5-Me (**2l**) substituents also underwent the reaction smoothly with high yields and good enantioselectivities (entries 13 and 14). It is worthy of mention that most of the products are solid and can be easily purified by recrystallization. For instance, the *ee* value of product **3lj** was enhanced to 99% after once recrystallization from petroleum ether. The absolute configuration of **3lj** was determined to be *S* by means of single crystal X-ray diffraction analysis (see Supporting Information for details).[13]

A plausible mechanism for present iron-catalyzed C–H functionalization of indoles is proposed, which is analogous with that of rhodium- and copper-catalyzed reaction (Scheme 1).[7] The diazoester was decomposed by iron catalyst to generate an iron carbene (step a), which reacted with indole to form a metal-associated zwitterionic intermediate **I** (step b). A proton migration from C-3 of the indole to the α-position of the ester took place to give the product and regenerate the iron catalyst (step c). The chiral induction is realized *via* an enantioselective proton migration. A study on the kinetic isotope effect (KIE = k_H/k_D) of the C-3 deuterium-labeled indole by competitive experiments was performed (see Supporting Information for details) and a KIE value of 5.06 was observed, which was comparable with that in the rhodium-catalyzed functionalization of aromatic C–H bonds.[14] The significant first order KIE value means that the proton transfer is most likely the rate-deter-



Scheme 1. Proposed mechanism.

mining step. Alternative mechanisms *via* a cyclopropanation-ring opening sequence or a concerted C–H insertion cannot be excluded at this stage. Additionally, the possibility that iron(II) activates the α-aryl-α-diazoacetate by association with its terminal nitrogen, which does not form an iron carbene intermediate, is also plausible. Further studies to identify the accurate mechanism are undergoing in this laboratory.

In summary, we have developed the first iron-catalyzed C–H functionalization of indoles with α-aryl-α-diazoacetates, which provided an efficient method for the construction of useful α-aryl-α-indolylacetate derivatives. The asymmetric version of this reaction was also accomplished with up to good enantioselectivities by using iron complexes of chiral spiro bisoxazoline ligands. This study further indicates a high potential for application of sustainable and environmentally benign iron catalysts in carbene transformations.

Experimental Section

General Procedure for the Fe-Catalyzed C–H Functionalization of Indoles

$Fe(ClO_4)_2 \cdot 4H_2O$ (2.5 mg, 0.0075 mmol), $NaBAr_F$ (8.5 mg, 0.009 mmol, 1.2 mol%), and 2 mL of 1,2-dichloroethane (DCE) were introduced into a Schlenk tube under argon. 1 mL of solution of TMEDA (0.009 M, 0.009 mmol, 1.2 mol%) in DCE was added. The resulting suspension was stirred under an argon atmosphere at room temperature for 4 h. A solution of methyl α-diazophenylacetate (**1a**) (158.4 mg, 0.9 mmol) and 1-benzylindole (**2a**) (155.3 mg, 0.75 mmol) in DCE (2 mL) was injected into the reaction mixture at 60 °C. The resulting mixture was stirred at 60 °C for the specified time, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (10:1, v/v).

General Procedure for the Fe-Catalyzed Asymmetric C–H Functionalization of Indoles

$Fe(ClO_4)_2 \cdot 4H_2O$ (5.0 mg, 0.015 mmol), (R_a,*S*,*S*)-**4a** (9.2 mg, 0.018 mmol, 6 mol%), $NaBAr_F$ (16.9 mg, 0.018 mmol, 6 mol%), and 3 mL of $CHCl_3$ were introduced into a

Schlenk tube under argon. The resulting suspension was stirred under an argon atmosphere at room temperature for 4 h. A solution of methyl α-diazophenylacetate (**1a**) (52.8 mg, 0.3 mmol) and 1-(*tert*-butyldimethylsilyl)indole (**2j**) (69.3 mg, 0.3 mmol) in 2 mL $CHCl_3$ was injected into the reaction mixture at 40 °C. The resulting mixture was stirred at 40 °C for the specified time, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (20:1, v/v).

Acknowledgements

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[12] (*S*,*S*)-Box [2,2′-(1-methylethyliene)bis(4,5-dihydro-4-phenyloxazole)]: 12 h, 72%, 10% *ee*; (*S*,*S*)-Pybox [2,6-bis(4,5-dihydro-4-phenyloxazole)pyridine]: 48 h, 64%, racemic.

[13] CCDC 821999 contains the supplementary crystallographic data for **3lj**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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