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Directing Groups

Development of Modifiable Bidentate Amino Oxazoline Directing Group for Pd-Catalyzed Arylation of Secondary C–H Bonds

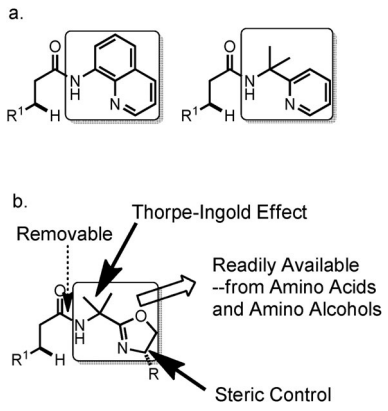
Kang Chen,[a] Zhao-Wei Li,[a] Peng-Xiang Shen,[a] Hong-Wei Zhao,[a] and Zhang-Jie Shi*[a, b]

Abstract: A novel bidentate α-amino oxazolinyl directing group has been developed. Different from previous directing groups, this newly designed directing group was easily prepared from amino acids and modified in structure. This auxiliary preferentially effects functionalization at secondary C(sp^3)–H bonds, rather than at aryl C(sp^2)–H bonds. The diastereoselectivity of direct arylation between geminal secondary C(sp^3)–H bonds in linear molecules has also been realized for the first time with a chiral directing group by remote chirality relay. Two diastereoisomers are produced with the same chiral source by changing the substituents of substrates and aryl halides.

Direct functionalization of C–H bonds has attracted much attention in the past several decades, because it affords the most straightforward pathway to producing valuable chemicals with higher atom- and step-economy compared to traditional synthetic methods, by avoiding the need for prefunctionalization.[1] Although many exciting achievements have been made in C(sp^2)–H functionalization,[2] in comparison, direct functionalization of inert C(sp^3)–H bonds is still challenging, as a result not only of the lack of interaction between aliphatic C–H bonds and metal catalysts, but also of the difficulty in controlling chemo-, site-, and stereoselectivities.[3] However, directing-group introduction has proven to be a successful strategy for solving such problems in aliphatic C–H bond activation.

In 2004, Sanford and co-workers developed the first Pd-catalyzed acetoxylation of aliphatic C–H bonds with *O*-methyl oximyl as the directing group.[4] Later on, a similar strategy was applied by Dong and co-workers.[5] Yu's group reported their pioneering works on the use of oxazoline rings and arylamides as unique directing groups for C(sp^3)–H functionalization.[6,7] Since 2005, Daugulis and co-workers have reported new bidentate directing groups that have proven significant in studies of C(sp^3)–H functionalization.[8] For example, these directing groups have been applied in alkoxylation,[9] amination,[10] alkynylation,[11] alkylation,[12] and oxidative borylation reactions.[13] Inspired by these important discoveries, chemists have made great efforts in recent years to design new chelating auxiliaries to promote C(sp^3)–H activation.[14] The groups of Chatani,[15] Chen,[16] Carretero,[17] Sahoo,[18] Shi,[19,20] Ackermann,[21] Ma,[22] and Zhao[23] have all provided innovative contributions to the design of auxiliaries. Besides Pd, other transition metals were also applied in such C(sp^3)–H bond functionalization reactions.[24]

Nevertheless, several challenges remain in this field: 1) although many currently known directing groups can promote direct functionalization of primary C–H bonds, only a limited number of directing groups are efficient for secondary C(sp^3)–H bond fuctionalization;[25] 2) most of the current effective bidentate directing groups contain heteroaryl rings that act as one of the coordinating sites (Scheme 1 a). Although such groups can be removed under different conditions, especially after modifications of the rings,[16] they offer few opportunities for useful structural modification or transformation into other moieties in the product molecules; 3) due to the planar structure of the heteroarenes, it seems impossible to meet the requirement of stereochemical control in secondary C–H functionalization.[26] In light of all of these limitations, novel auxiliaries that demonstrate easy removability, potential transformability, and the ability to simultaneously control chemo-, regio-, and stereochemistry are highly appealing.



Scheme 1. Examples of previously reported bidentate directing groups (a) and design of the bidentate α-amino oxazoline directing group for diastereoselective arylation of secondary C–H bonds (b).

[a] *K. Chen, Z.-W. Li, P.-X. Shen, Dr. H.-W. Zhao, Prof. Dr. Z.-J. Shi*
Beijing National Laboratory of Molecular Science (BNLMS) and
Key Laboratory of Bioorganic Chemistry and Molecular Engineering of the Ministry of the Education, College of Chemistry and Green Chemistry Center
Peking University, Beijing, 100871 (China)
E-mail: zshi@pku.edu.cn

[b] *Prof. Dr. Z.-J. Shi*
State Key Laboratory of Organometallic Chemistry
Chinese Academy of Science, Shanghai, 200032 (China)

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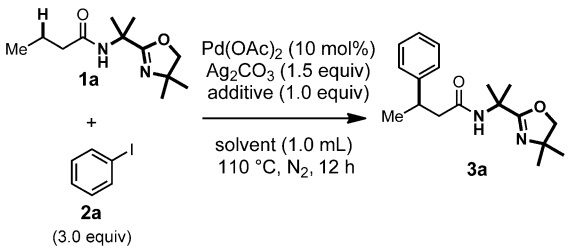
Oxazoline has been identified as a competent removable directing group in primary C(sp^3)–H functionalization, indicating that it is a promising surrogate for pyridine or quinoline moieties.[6] Furthermore, chiral oxazoline rings are readily prepared from the corresponding amino alcohols, which can potentially control the diastereoselectivity in the secondary C(sp^3)–H functionalization. As reported, the geminal dimethyl structural unit may be important to control the bite angle with Pd according to the Thorpe–Ingold's effect,[27] which may enhance the chelation effect and the stability of metallacycles. Inspired by those previous successes, we now design the α-amino oxazolinyl moiety to promote both reactivity and selectivity in secondary C–H arylation (Scheme 1 b). In this development, chemo-, regio- as well as diastereoselectivity are well controlled by the newly designed bidentate directing group.

Our initial studies concerned the screening of reaction conditions for the coupling between substrate **1 a** and phenyl iodide **2 a** (Table 1). As expected, **1 a** was arylated at the secondary C–H bonds in presence of $Pd(OAc)_2$ as the catalyst

Table 1. Optimization of reaction conditions.

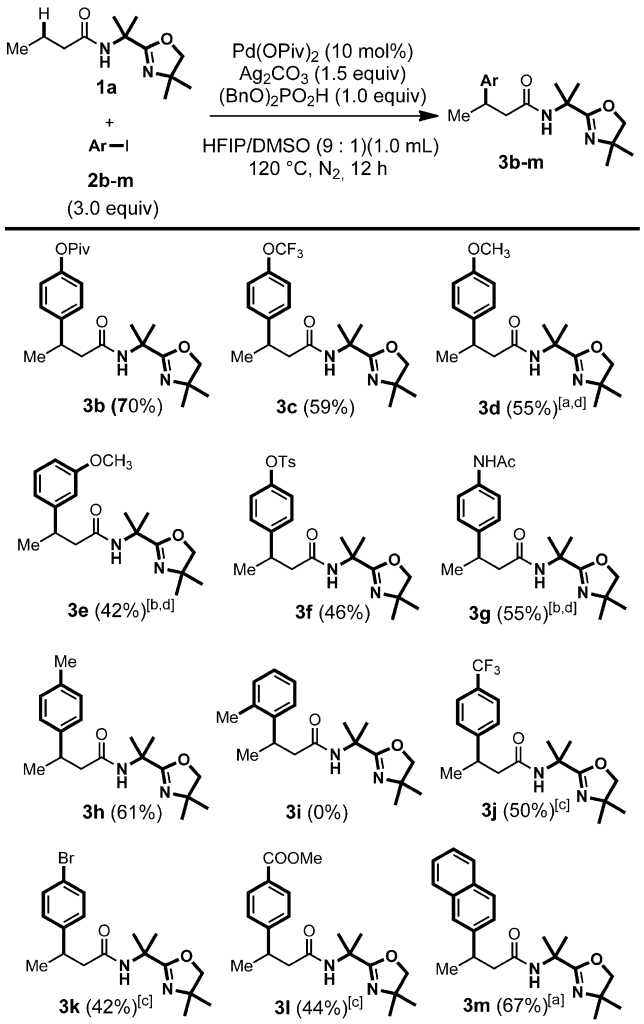


Entry	Additive	Solvent	Yield [%][a]
1	AcOH	*t*-AmylOH	28
2	PivOH	*t*-AmylOH	32
3	$(BnO)_2PO_2H$	*t*-AmylOH	43
4	$(BnO)_2PO_2H$	*t*-BuOH	48
5	$(BnO)_2PO_2H$	CF_3CH_2OH	52
6	$(BnO)_2PO_2H$	HFIP	55
7[b]	$(BnO)_2PO_2H$	HFIP	58
8	$(BnO)_2PO_2H$	HFIP/DMSO (9:1)	68
9	$(BnO)_2PO_2H$	HFIP/DMSO (8:2)	47
10[c]	$(BnO)_2PO_2H$	HFIP/DMSO (9:1)	72
11[d]	$(BnO)_2PO_2H$	HFIP/DMSO (9:1)	76
12[c,d]	$(BnO)_2PO_2H$	HFIP/DMSO (9:1)	80 (66)[e]

[a] Unless otherwise stated, reactions were carried out at 0.1 mmol scale. Yields were determined by ^1H NMR spectroscopy with anisole as the internal standard; [b] 5.0 equiv of DMSO was added; [c] $T = 120\,^{\circ}C$, [d] $Pd(OPiv)_2$ was the catalyst; [e] yield of isolated product of a 0.2 mmol-scale reaction in 1.0 mL solvent. AcOH = acetic acid; PivOH = pivalic acid; $(BnO)_2PO_2H$ = dibenzyl phosphate; *t*-AmylOH = 2-methyl-2-butanol; DMSO = dimethyl sulfoxide; HFIP = hexafluoro-2-propanol.

(Table 1, entry 1). Inspired by the results of Chen's group,[28] we also tested dibenzyl phosphate ($(BnO)_2PO_2H$) as an additive, finding it to be more effective than carboxylic acids (entries 1–3). In screening of solvents, we found that fluoroalcohols, particularly hexafluoro-2-propanol (HFIP), led to improved yields (Table 1, entries 3–6). Further investigations revealed that addition of DMSO to the solvent was also critical for this reaction (Table 1, entries 7–9). Finally, when we used $Pd(OPiv)_2$ as the catalyst, the substrate was completely converted and the optimal result was obtained at a higher reaction temperature (Table 1, entries 10–12). To investigate the critical effect of the geminal dimethyl groups, we replaced the dimethyl linkage of **1 a** with different aliphatic rings. As predicted, none of these substrates were comparable with **1 a** and the yields decreased dramatically. The lack of methyl groups also led to inferior results in the arylation reaction (see the Supporting Information).

We further investigated the scope of aryl iodides under the optimal conditions (Scheme 2). Various protected iodophenols

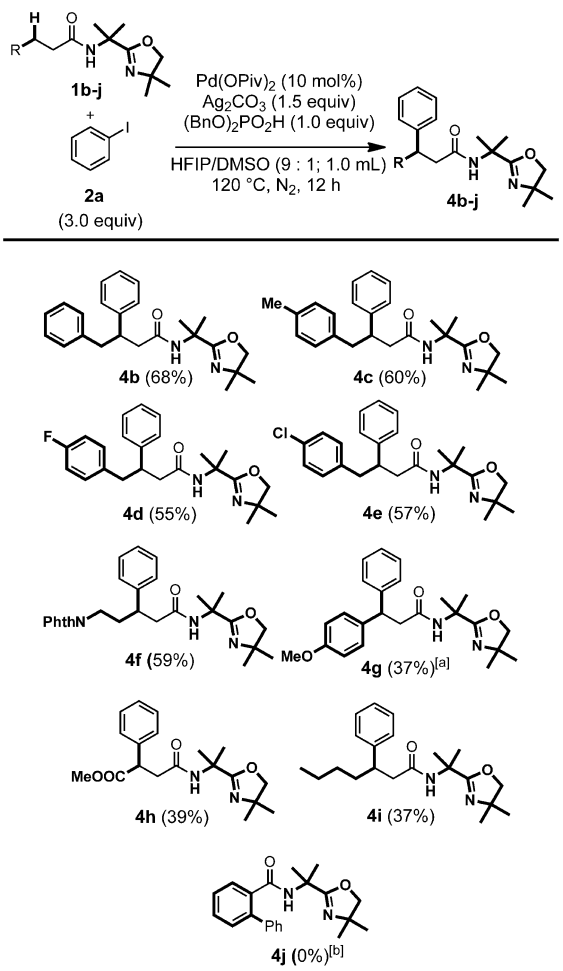


Scheme 2. Pd-catalyzed secondary C(sp^3)–H arylation of substrate **1 a** with different aryl iodides **2 b**–**m**. Reactions were carried out at 0.2 mmol scale in 1.0 mL solvent for 12 h unless otherwise specified. Yields of isolated product are given. [a] HFIP/DMSO (1.8 mL:0.2 mL); [b] HFIP/DMSO (1.8 mL:0.3 mL); [c] HFIP/DMSO (0.9 mL:0.15 mL); [d] $t = 24$ h.

gave moderate to good yields (**3 b**–**f**). The acetamide-substituted aryl iodide was also tolerated, leaving the aryl C–H bonds unaffected (**3 g**). The reaction was quite sensitive to steric hindrance. For example, 4-iodotoluene reacted smoothly with **1 a**, whereas 2-iodotoluene completely failed to give the desired product (**3 h** and **3 i**). Reactions with electron-deficient aryl iodides gave reasonable results, albeit with low substrate con-

version (**3j–l**). To our delight, other functional groups, such as ester and bromide substituents, survived in the reaction system, offering opportunities for further orthogonal transformations. Besides phenyl iodide derivatives, 2-iodonaphthalene was also verified as an efficient coupling partner, giving **3m** in reasonable yield.

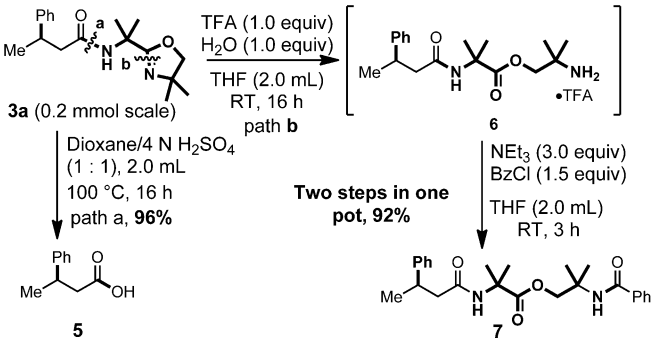
Next, we examined different amide derivatives (Scheme 3). 4-Arylbutanamide derivatives reacted smoothly with phenyl iodide to generate 3,4-diarylbutanamides, leaving the more active benzylic position unaffected. Either electron-donating or



Scheme 3. Pd-catalyzed secondary C(sp^3)–H arylation of amide derivatives **1b–j** with phenyl iodide **2a**. Reactions were carried out at 0.2 mmol scale for 12 h unless otherwise specified. Yields of isolated product are given. [a] 4-iodoanisole was used as the coupling partner and the reaction time was 24 h; [b] 76% of starting material was recovered.

electron-withdrawing groups located on the phenyl group gave comparable yields (**4b–e**). Halides also survived the reaction well (**4d** and **4e**). Phthaloyl-protected 5-aminopentanamide was also a suitable substrate and an acceptable yield of **4f** was obtained. β-Arylpropanamide showed a relatively lower reactivity (**4g**). The monoamide of a 1,4-diacid derivative exhibited poor reactivity, although a sole regioisomer was isolated, showing the importance of the directing group (**4h**). A substrate with a longer carbon chain was also a successfully arylated, albeit with a decreased yield (**4i**). Surprisingly, this newly designed directing group was completely ineffective in C(sp^2)–H arylation of an aryl amide derivative and only the corresponding starting material (**1j**) was recovered. This specific feature in C(sp^3)–H bond chemoselectivity was distinct from many other reported directing groups.

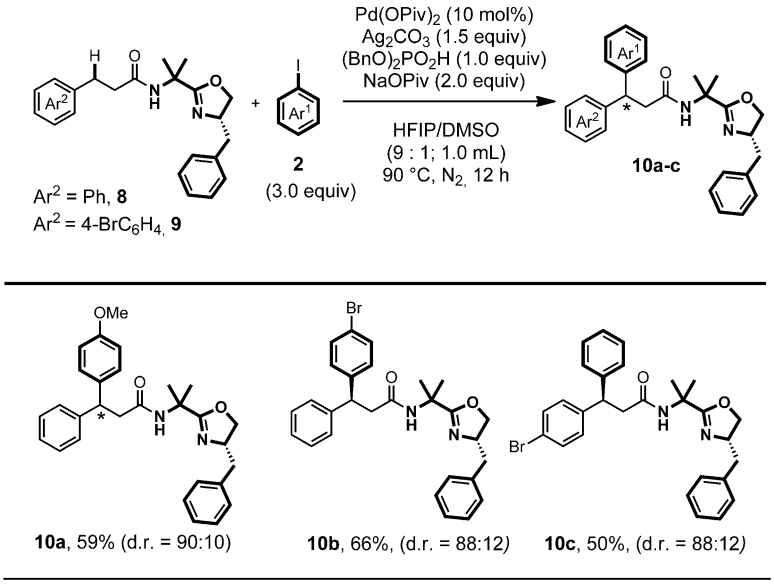
Owing to the multiple active sites of the α-amino oxazoline auxiliary, it was possible to carry out different transformations upon it after the C(sp^3)–H arylation. Actually, this directing group was successfully removed by hydrolysis under acidic conditions. The corresponding acid **5** was obtained in an excellent yield (Scheme 4). Alternatively, the oxazoline ring could be opened under very mild conditions to afford the amine trifluoroacetate intermediate **6**. This intermediate easily underwent different transformations, such as benzoylation, in one pot (Scheme 4). These results might be built upon to create future designs of transformable directing groups.



Scheme 4. Auxiliary cleavage and transformation.

As designed, the introduction of the oxazolinyl group afforded the capability to input chiral elements. Thus, we set out to prove our concept by exploring chiral oxazolines to control the diastereoselectivity of secondary C(sp^3)–H arylation. From commercially available L-amino alcohols, substrates containing chiral auxiliaries were prepared. Unfortunately, the diastereoselectivity was very low under the developed conditions (see the Supporting Information). According to the substrate structure, we considered that the chiral center was rather far away from the reactive site; too far in principle to directly control the diastereoselectivity by steric hindrance.

According to the previous studies, the concerted metalation–deprotonation (CMD) pathway was proposed to facilitate C–H activation.[29] We hypothesized that the orientation of the counterion participating in the CMD pathway could be induced by the chirality of the oxazoline ring, which would help to overcome the long distance between the directing group and the secondary C–H bond. The resultant enhancement in the steric hindrance of the counterions would thus lead to better diastereoselectivity. Indeed, when we used substrate **8** (Scheme 5), product **10a** was obtained with good diastereoselectivity (d.r. = 90:10) after the addition of NaOPiv. In agreement with the former result, the arylation only took place at

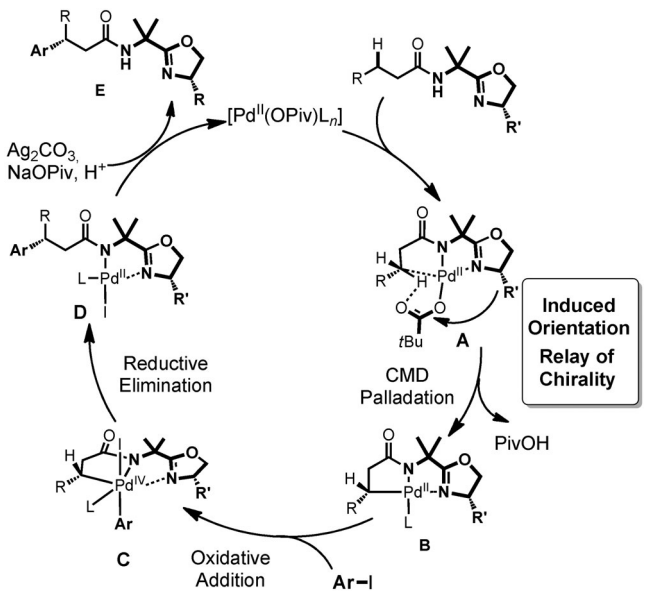


Scheme 5. Exploration of diastereoselective secondary C(sp^3)–H arylation by chiral directing groups. All reactions were carried out at 0.1 mmol scale. The d.r. values of the products were determined from the e.r. values of corresponding esters, which were obtained after the cleavage of the chiral auxiliaries and esterification.

the benzylic C(sp^3)–H position, while the phenyl group on the chiral auxiliary remained unaffected.

When we used 4-bromo-1-iodobenzene as the coupling reagent, we assigned the absolute configuration at the benzylic site as *S* in the major diastereoisomer by comparing the analytical data with references (**10b**).[30] This result was beneficial for us to understand the stereochemical process in the arylation reaction. Furthermore, we could also prepare the product with *R* configuration at the benzylic site with the same chiral auxiliary by simply exchanging the aryl groups between the substrate and aryl iodide (**10c**). Notably, this reaction represents the first case in which diastereoselective intermolecular coupling takes place between two secondary geminal C(sp^3)–H bonds in linear molecules without any chiral center adjacent to the reaction site.[31]

In light of previous studies and our observations on diastereoselective control, we propose the mechanism depicted in Scheme 6. The substrate first coordinates to Pd, positioning the Pd center close to the corresponding C(sp^3)–H bond to form the intermediate **A**, which determines the diastereoselectivity of the whole reaction process. In the C–H bond cleavage step, the chiral space formed by the chiral auxiliary induces the orientation of ligands on the Pd center. Thus, the sterically hindered pivalate anion participates in the CMD process, coordinating to Pd on the opposite side to the R′ group to minimize steric repulsion. For the same reason, the R group adjacent to the secondary C(sp^3)–H bond is oriented away from the pivalate anion. This relayed effect facilitates chirality transfer from the remote auxiliary to the reaction site and eventually leads to the observed diastereoselectivity.[32] The aryl iodide then undergoes oxidative addition to the intermediate **B** to generate the Pd^{IV} species **C**. Finally, reductive elimination takes place to form the desired product and the Pd catalyst is regenerated to complete the catalytic cycle.



Scheme 6. Proposed mechanism.

In conclusion, we have developed a modifiable amino oxazoline directing group to facilitate the Pd-catalyzed secondary C(sp^3)–H arylation of amides. This auxiliary exhibited multiple functionalities to promote both reactivity and site selectivity. Chiral auxiliaries were used to achieve the asymmetric secondary C(sp^3)–H arylation by relayed chirality transfer. The designed directing group could be simply removed or converted into other useful functional groups. Efforts into improving both the reactivity and diastereoseletivity of this auxiliary-assisted secondary C(sp^3)–H functionalization are currently underway in our laboratory.

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Keywords: arylation · directing groups · diastereoselectivity · oxazolines · palladium

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[25] Most bidentate auxiliaries derived from amines are limited to activating the primary C–H bond (see refs. [15–18] and [20–23]), whereas only a few bidentate auxiliaries derived from carboxylic acids are competent for secondary C–H functionalization (see refs. [8] and [19]).

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COMMUNICATION

Directing Groups

*K. Chen, Z.-W. Li, P.-X. Shen, H.-W. Zhao, Z.-J. Shi**

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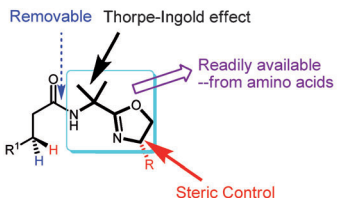
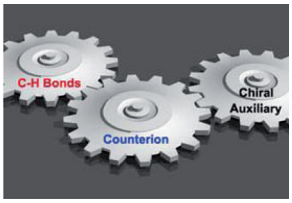
Development of Modifiable Bidentate Amino Oxazoline Directing Group for Pd-Catalyzed Arylation of Secondary C–H Bonds





A new direction: A multifunctional amino oxazoline directing group that is readily available from amino acids, has been developed, which can induce chemo-, regio- and diastereoselectivity in secondary C(sp^3)–H arylation reactions. Furthermore, this directing group is removable and modifiable. Steric control and counterions play important roles in the relayed chirality transfer.