Regio- and enantioselective remote hydroarylation using a ligand-relay strategy

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The design of a single complicated chiral ligand to well-promote each step of an asymmetric cascade reaction is sometimes a formidable challenge in transition metal catalysis. In this work, a highly regio- and enantioselective Ni-catalysed migratory hydroarylation relay process has been achieved with the combination of two simple ligands, one which accomplishes chain-walking and the other causing asymmetric arylation. This formal asymmetric C(sp³)−H arylation provides direct access to a wide range of structurally diverse chiral 1,1-diarylalkanes, a structural unit found in a number of bioactive molecules. The value of this strategy was further demonstrated by the Ni-catalysed migratory asymmetric 1,3-arylboration.
The synergistic combination of olefin isomerization and cross-coupling, nickel-catalysed migratory hydrofunctionalization of alkenes, has emerged as a complementary and versatile platform that can realize a wide variety of remote C(sp³)–H functionalizations. So far, much progress has been made in the NiH-catalysed asymmetric ipso-hydrofunctionalization of alkenes. However, designing a chiral ligand for nickel that could promote both chain-walking and subsequent regio- and enantioselective reductive coupling at a remote position remains a formidable challenge (Fig. 1a).

Overcoming the limitation of single metal catalysis [ML], multimetallic catalysis [MLAL & MLBL] provides a complementary strategy that has been well exploited. The alternative reaction using multiligands has remained largely underexplored. Pioneering work in this area has shown that multiligand based binary ligand complexes [MLAL] could be formed and are more reactive catalysts. A catalyst mixture [MLA & MLA] formed by Buchwald et al. to broaden the substrate scope of a system using a single catalyst [MLA]. Instead of designing a complex ligand, another unique mode of employing multiligands is to undergo multiligand relay catalysis via dynamic ligand exchange in cases where a single ligand fails to selectively or efficiently promote all the steps of the transformation. In this attractive but largely underexplored pathway, each ligand is only required to promote partial steps of the catalytic cycle. This concept was preliminarily explored by White’s group in the Pd-catalysed non-asymmetric allylic oxidation system while using stoichiometric amount of benzoquinone or DMSO as another ligand for functionalization step. Very recently, Fu et al. and Mauleón et al. demonstrated that the exchange of dynamic mutiligands with metals could be used to sequentially promote different steps in Cu-catalysed relay reactions. At the same time, our laboratory successfully introduced this concept to the nickel-catalysed asymmetric migratory hydrofunctionalization process, wherein the entire catalytic cycle could be subsequently promoted by an achiral chain-walking ligand and a structurally simple chiral asymmetric coupling ligand (Fig. 1b). Pursuing this theme, we hypothesized that migratory asymmetric hydroarylation which consists of an achiral ligand (L) promoting chain-walking and a chiral ligand (L*)

**Fig. 1 Design plan:** Synergistic combination of a chain-walking ligand (L) and an asymmetric arylation ligand (L*) to access chiral 1,1-diarylalkanes.

- **a** NiH catalyzed remote hydrofunctionalization: Stereochemistry is still a challenging issue.
- **b** Multiligand-relay catalysis: Solution for asymmetric remote hydrofunctionalization.
- **c** MLRC (L/L*): Asymmetric remote hydroarylation to access chiral 1,1-diarylalkanes.

**Fig. 1b** MLRC (L/L*): Asymmetric remote hydroarylation to access chiral 1,1-diarylalkanes.
promoting asymmetric arylation at benzylic position\textsuperscript{61–65} could be possible, leading to the facile synthesis of an enantioenriched 1,1-diaryllkane, a biologically active pharmacophore (Fig. 1c).

In this work, we describe a highly regio- and enantioselective Ni-catalysed migratory hydroarylation relay process enabled by a multiligand relay catalysis strategy. By synergistic combination of a simple ligand for chain-walking and a known ligand for asymmetric arylation, a wide variety of enantioenriched 1,1-diaryllkanes can be rapidly obtained under mild conditions.

**Results and discussion**

**Reaction design and optimization.** Our initial investigation focused on the enantioselective remote hydroarylation of 4-phenyl-1-butene (1a) with 4-iodoanisole (2a) (Fig. 2). It was found that NiCl\textsubscript{2}·glyme (glyme = ethylene glycol dimethyl ether) and the synergistic combination of a chain-walking ligand (L, 2,9-dimethyl-1,10-phenanthroline) and an asymmetric arylation ligand (L\textsuperscript{5}, (4 R,4’R)-1,1’-bis(3-(tert-butyl)-phenyl)-4,4’-di(heptan-4-yl)-4’,5’,5’-tetrahydro-1H,1’H-2,2’-biimidazole)\textsuperscript{31} with DMMS (dimethoxymethylsilane) could afford the desired migratory product 1-methoxy-4-(1-phenylbutyl)-benzene (3a) as a single regioisomer in 84% isolated yield and with 95% enantiomeric excess (ee) (entry 1). Control experiments revealed that these two ligands are both essential for simultaneous control of the regio- and stereochemistry, and poor regioselectivity was observed in the absence of the chain-walking ligand (entries 2–4). Importantly, lowering the loading of the chain-walking ligand to 0.4 mol% had little impact on the overall performance (entry 5). Increasing the chain-walking ligand loading and decreasing the arylation ligand loading led however to a moderate decrease of both the yield and the enantioselectivity (entry 6). An alternative chain-walking ligand (L1) was found to be competent but less effective than L (entry 7). Evaluation of arylation ligands revealed that L\textsuperscript{5} provided the highest ee (entry 1 vs. entries 8–10). Diminished yields were

| entry | deviation from standard conditions | yield of 3a (%)\textsuperscript{a} | rr\textsuperscript{†} | ee\textsuperscript{‡} |
|-------|-----------------------------------|-----------------------------------|---------------------|---------------------|
| 1     | none                              | 90 (84)                           | 99:1                | 95                  |
| 2     | w/o L                             | 52                                | 68:32               | 95                  |
| 3     | w/o (R,R)-L\textsuperscript{*}    | 4                                 | –                   | –                   |
| 4     | w/o (R,R)-L\textsuperscript{*}, 6 mol% L used | 77 | 99:1 | – |
| 5     | 0.4 mol% L, 6 mol% (R,R)-L\textsuperscript{*} | 86 | 97:3 | 96 |
| 6     | 3 mol% L, 3 mol% L\textsuperscript{*} | 77 | >99:1 | 78 |
| 7     | L1 instead of L                   | 76                                | 97:3                | 94                  |
| 8     | L1\textsuperscript{*} instead of L\textsuperscript{*} | 91 | 99:1 | 91 |
| 9     | L2\textsuperscript{*} instead of L\textsuperscript{*} | 70 | 96:4 | 80 |
| 10    | L3\textsuperscript{*} instead of L\textsuperscript{*} | 46 | 94:6 | 55 |
| 11    | NiL\textsubscript{5} instead NiCl\textsubscript{2}·glyme | 80 | 99:1 | 94 |
| 12    | PMHS instead DMMS                 | 70                                | 98:2                | 95                  |
| 13    | K3PO\textsubscript{4}·H\textsubscript{2}O instead KF | 79 | 99:1 | 93 |
| 14    | DMPU only                         | 42                                | 96:4                | 92                  |
| 15    | toluene only                      | <5                                | –                   | –                   |
| 16    | ArBr instead of ArI               | 74                                | 99:1                | 95                  |

Fig. 2 Variation of reaction parameters. *Yields were determined by gas chromatography (GC) analysis using n-dodecane as the internal standard, the yield within parentheses is the isolated yield and is an average of two runs (0.20 mmol scale). †Regiosomeric ratio (rr) represents the ratio of the major (1,1-diaryllkane) product to the sum of all other isomers as determined by GC and GC-MS analysis. ‡Enantioselectivities were determined by chiral HPLC analysis, the absolute configuration of 4t was determined by X-ray crystallography, and the configurations of the remaining products were assigned by analogy. Glyme ethylene glycol dimethyl ether, DMMS dimethoxymethylsilane, DMPU N,N’-dimethylpropyleneurea, Tol toluene, PMP p-methoxyphenyl, PMHS polymethylhydrosiloxane.
obtained when using other nickel sources (entry 11) or employing other silanes (entry 12) or replacing K₃PO₄·H₂O as base (entry 13). The use of a single solvent led to either diminished yield (entry 14) or almost complete failure of the reaction (entry 15). Notably, a slightly reduced yield was obtained when a less reactive aryl bromide was used (entry 16).

**Substrate scope.** With the well-established conditions in hand, the scope and generality of the reaction were evaluated. As illustrated in Fig. 3, a wide variety of aryl and heteroaryl iodides or bromides are tolerated. In general, the less reactive aryl bromides resulted in a slightly decreased yield (3a, 3b, 3f, 3h, 3k, and 3l). The reaction proceeded well with both electron-rich (3b–3e) and electron-withdrawing aryl halides (3f–3q). A variety of functional groups are readily accommodated, including ethers (3a, 3e–3g, 3i, and 3s), esters (3b, 3k), a Boc carbamate (3e), an amide (3d), a trifuoromethyl group (3j), a nitrile (3l), an aryl fluoride (3m), and an aryl chloride (3n). Notably, under these exceptionally mild reaction conditions, sensitive functional groups such as aryl triflate (3o) commonly used for subsequent complementary cross-coupling, and readily reduced aldehydes (3p) and ketones (3q) were all unaffected. Heterocycles such as indole (3r) and pyridine (3s and 3f) are also competent coupling partners. However, o-substituted (hetero)aryl halides gave lower yields under current conditions.

We next explored the scope of alkenes (Fig. 4). As shown in Fig. 4a, a wide range of terminal aliphatic alkenes bearing a remote aryl (4b–4n, 4s, 4t) or heteroaryl (4o–4l) group undergo asymmetric migratory hydroarylation smoothly, regardless of the chain length between the C–C bond and the remote aryl group. In general, a slightly increased loading of the chain-walking ligand is beneficial for alkenes substrates with a long chain (4m). A variety of substituents on the remote aromatic ring, including both electron-donating (4c–4e) and electron-withdrawing (4f–4l) substituents, are all well-tolerated. Notably, the 1,1-disubstituted alken (4n) is also a suitable substrate, although the migratory product was obtained in decreased yield. As shown in Fig. 4b, unactivated internal alkenes are also suitable substrates (4u–4u”). Both E (4y, 4z) and Z (4a”) alkenes, as well as E/Z mixtures (4u–4x”) were suitable substrates. In addition, a range of different substituents at the other terminus of the alkyl chain, even with a heteroatomic substituent (4x–4z), were all well-tolerated, and arylation at benzylic position was still preferred.

**Application.** Benefiting from the chain-walking catalysis, isomeric mixtures of olefins could be used directly to produce the enantioenriched product (4m) in a regioconvergent fashion (Fig. 5a). The current multiple ligand catalysis could also be applied to migratory difunctionalization of alkenes 66. As shown in Fig. 5b, a nickel-catalysed 1,3-arylboration reaction was...
Mechanistic investigation. A series of mechanistic experiments were carried out to understand the relay process. As shown in Fig. 6a, isomeric mixtures of olefins could be produced during the reaction process, an observation that is consistent with a fast chain-walking step. As shown in Fig. 6b, in the absence of cross-coupling partner, control experiment revealed that the alkene isomerization could also proceed smoothly with dual ligands or with a single chain-walking ligand. These results indicate that chain-walking precedes arylation without the participation of cross-coupling partner. In contrast, only a very small quantity of isomerized alkenes was observed while using arylation ligand \( L^* \) alone. This observation is consistent with the conclusion that the chain-walking process is mainly promoted by achiral chain-walking ligand \( L \). To probe whether hydronicellation is the enantio-determining step, isotopic labelling experiments of a cyclic styrene \( 1b \) substrate were carried out using a racemic ligand \( L^2 \) to promote NiBpin insertion/chain-walking together with the asymmetric arylation ligand \( L^3 \) which promotes asymmetric arylation. The desired migratory chiral products (7a–7h) were obtained with high regioselectivity and excellent ee.

Fig. 4 Substrate scope of alkene coupling component. Under each product is given yield in percent, regioisomeric ratio (rr), and either the enantioselectivities (ee) or the diastereomeric ratio (dr). Yield, rr and ee are as defined in Fig. 3 legend. *2% \( L \) used. †0.4% \( L \) used. ‡Diastereoselectivity (dr) determined by \(^1\)H NMR analysis of the crude reaction mixture.
additions involving chiral ligand via TS1-R and TS1-S are much easier. The overall barrier for the formation of chiral Ni(III) species INT2-R is 16.2 kcal/mol via TS1-R, which is 4.2 kcal/mol lower than that for the oxidative addition of achiral alkynickel(I) via TS1-a (20.4 kcal/mol). For two competing enantioselective transition states TS1-R and TS1-S, there is a 1.8 kcal/mol preference toward (R)-intermediate, corresponding to a 91% ee value of the final product at 298 K. In TS1-R, a less sterically demanding phenyl is placed close to the bulky isopropyl group of ligand, while in TS1-S, it is the ethyl group that generates steric repulsion with the bulky isopropyl group (highlighted in pink, Fig. 7). Meanwhile, the unreacted INT1-S can be rapidly converted to INT1-R via a reversible ligand exchange, transmetallation and alkene insertion process (see Supplementary Fig. 5). After the irreversible formation of chiral Ni(III) intermediate INT2-R, the following reductive elimination via TS2-R to yield product is very facile with a barrier of only 4.1 kcal/mol, which is much lower than the possible homolysis via TS3-R<sup>−</sup><sup>2</sup>. Therefore, the chiral bisimidazoline ligand controlled the Ni(I)/Ni(III) oxidative addition with aryl iodide, which is the rate-

**Methods**

**General procedure (A) for the regio- and enantioselective C(sp<sup>2</sup>)<sup>−</sup>−H arylation.** In a nitrogen-filled glove box, to an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar was added NiCl<sub>2</sub>·glyme (2.2 mg, 5.0 mol%), KF (23.2 mg, 0.44 mmol) followed by DME (0.4 mL) with a sealed cap, then NaOEt/H<sub>2</sub>O (2.0 equiv) and 1,3-arylboration ligand (1.4, 0.20 M). The mixture was then stirred at room temperature (22 ~ 26 °C) for 1 h. After reaction was complete, the reaction mixture was directly filtered through a short pad of silica gel (using EtOAc in petroleum ether) to give the crude product. The crude was purified by column chromatography on silica gel (33:1 hexanes:EtOAc). The ee values were determined by chiral HPLC analysis using chiral stationary phases.
Fig. 7 Computational study of the asymmetric arylation. Computed at SMD(DCM)-(U)M06-2/6-31+G(d,p)[SDD for Ni and I]. Values are relative Gibbs free energies in kcal/mol. Coloured atoms in graphics: grey, C; white, H; red, O; blue, N; green, Ni; purple, I. Distances are in angstroms.

Data availability
The authors state that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its supplementary information files, and also are available from the corresponding author.

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