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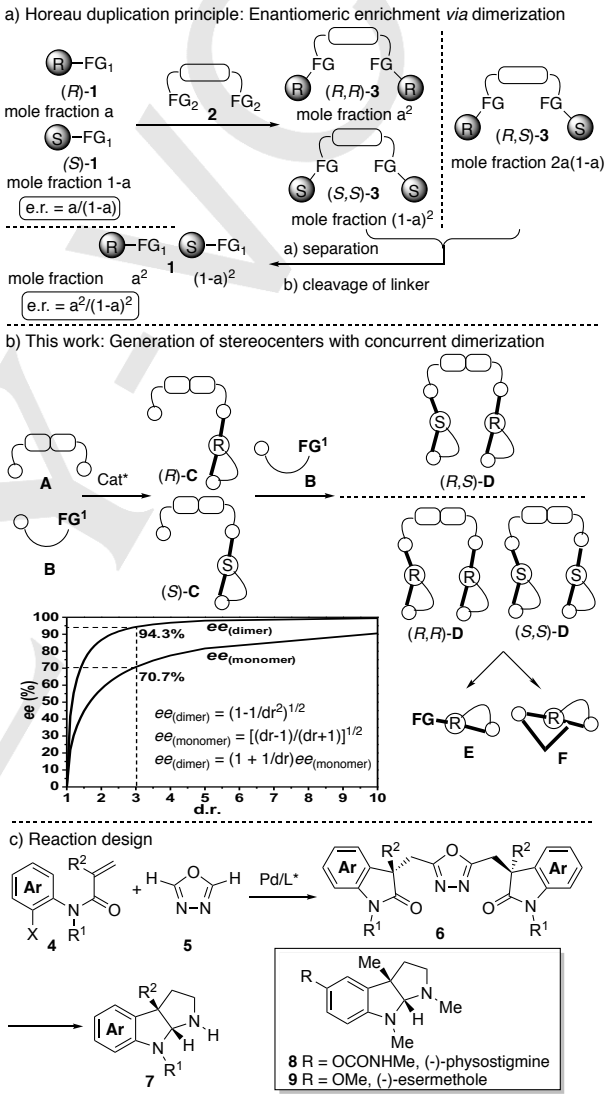
Catalytic Enantioselective Double Carbopalladation/C-H Functionalization with Statistical Amplification of Product Enantiopurity: A Convertible Linker Approach

Shuo Tong, Aurore Limouni, Qian Wang, Mei-Xiang Wang and Jieping Zhu*

Abstract: *We demonstrated that combining a catalytic enantioselective reaction with dimerization in a single operation is an efficient way to upgrade the enantiomeric excesses (ee) of the product. Palladium-catalyzed reaction of N-(2-iodophenyl)-N-methyl methacrylamide derivatives with oxadiazole afforded, via a double enantioselective carbopalladation/intermolecular direct heteroarene C-H alkylation cascade, homodimers in good yields with excellent ee. The dimer was subsequently elaborated to the monomer in which the linker (oxadiazole) was incorporated into the target product.*

Enantioenriched compounds are routinely prepared by resolution of racemates, enantioselective reactions or from chiral pool. Many enantioselective transformations leading to the products with high *ee* have been developed during the past 50 years. However, there were still some reactions whose enantioselective versions provided products with less than satisfactory *ee* and additional purification or synthetic manipulations were therefore needed in order to upgrade the enantiopurity of the target.[1] Among those *ee* amplification methods without recurring chiral catalyst or reagent was the statistical enantiomeric enrichment via dimerization pioneered by Langenback[2] and Horeau.[3-5] It consists of reaction of a chiral non-racemic compound **1** with an achiral bifunctional linker **2** to afford a mixture of *(R,R)*-**3**/*(S,S)*-**3** and *(R,S)*-**3** dimers. Isolation of the *(R,R)*-**3**/*(S,S)*-**3** pair followed by removal of the linker regenerates compound **1** with increased enantiopurity. Assuming that there was no kinetic resolution in the dimerization process and the e.r. of the initial compound was a/(1-a) (a represents the mole fraction of the major enantiomer in its initial composition), then the e.r. of the recovered compound **1** after dimerization and removal of the linker will be upgraded to $a^2/(1-a)^2$. The price to be paid is the partial loss of the materials in the form of *meso* diastereomer (Scheme 1a). The so-called Horeau duplication principle[6-8] has since been successfully used for the *ee* amplification of non-racemic compounds[9] and the *ee* determination via the *in situ* dimerization with an achiral bifunctional linker.[10] A prerequisite to apply such a strategy is that the prochiral substrate must contain an additional functional group that can be used for the dimerization and two extra steps, *i.e.* introducing and cleaving the linker, would have to be added to the reaction sequence. Enantioselective reaction on achiral substrates having multiple prochiral functions have also been exploited to increase the *ee* of the desired products.[11-12]



Scheme 1. Horeau Duplication Principle: Concept and Reaction Design

We propose herein a novel approach combining the enantioselective reaction with the dimerization in a single operation. As illustrated in Scheme 1b, reaction of substrate **A** with a bifunctional substrate **B** under catalytic enantioselective conditions would produce firstly the monomer **C** in which two chemical bonds were formed, one for generating a stereocenter from the prochiral function (FG^1) while the other for connecting with the linker. Reaction of **C** with another molecule of **B** following the same domino sequence would afford a mixture of diastereomers *(R,R)*-**D**/*(S,S)*-**D** and *(R,S)*-**D**. Separation of the

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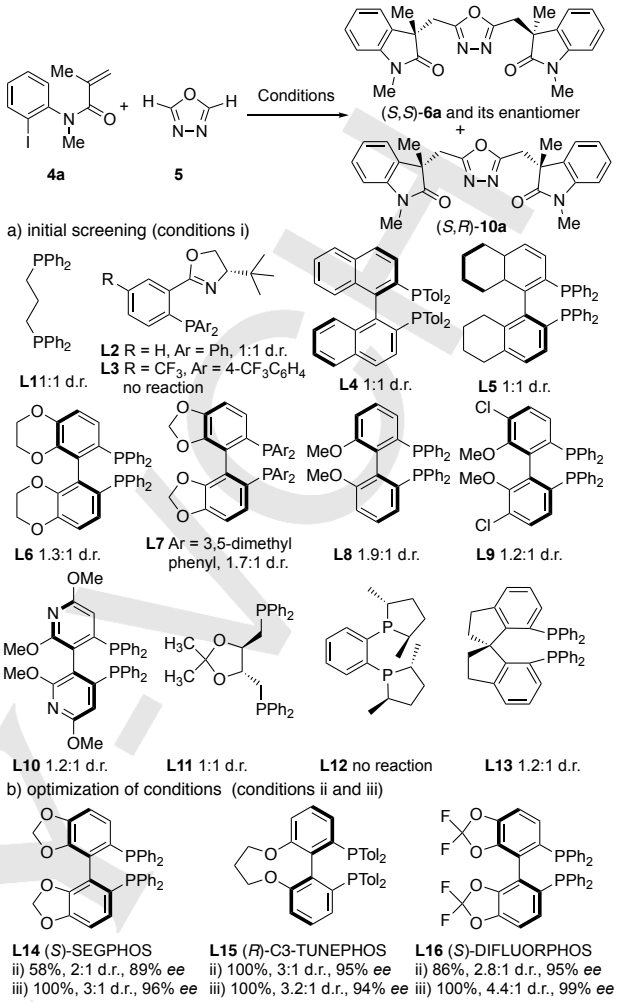
(*R*,*R*)-**D**/(*S*,*S*)-**D** pair from the (*R*,*S*)-**D** diastereomer followed by removal of the linker would afford two molecules of monomer with an *ee* higher than that obtained by a single enantioselective process. Two options exist for this last step: a) simple cleavage of the linker to reveal the target monomer **E** and b) the linker contains latent functions that could be elaborated into a more complex monomeric structure **F**. Assuming that substrate control in the second asymmetric reaction (from **C** to **D**) was minimum, one could then calculate the *ee* of the dimer and the monomer from the d.r. value of the dimers according to the following equations: $ee_{(dimer)} = (1\text{-}1/dr^2)^{1/2}$, $ee_{(monomer)} = [(dr\text{-}1)/(dr+1)]^{1/2}$, $ee_{(dimer)} = (1 + 1/dr)ee_{(monomer)}$ (see SI for algebraic solution). The d.r. value, measurable by ^{1}H NMR spectroscopy or by HPLC without recurring the chiral stationary phase, could therefore be used as an indicator of the enantioselectivity of the reaction. A moderate d.r. of 3/1 would indicate that the *ee* of the compound **D** could reach 94.3%, while that of **C** would be only 70.7% *ee* (Scheme 1b). As a proof of concept, we report herein a Pd-catalyzed enantioselective double carbopalladation/C-H functionalization of acetanilide **4** with oxadiazole (**5**) for the synthesis of bis-oxindoles **6** and its subsequent conversion to two molecules of pyrroloindolines **7**, important structural motif found in natural products and medicinally relevant compounds. For example, (-)-physostigmine (**8**), isolated from *calabar bean*, and (-)-esermethole (**9**) are reversible cholinesterase inhibitors with proving medicinal application.[13]

The domino carbopalladation/nucleophilic capture is a powerful strategy for the synthesis of medicinally relevant heterocycles.[14] However, the development of enantioselective version is highly challenging.[15-18] *N*-(2-Iodophenyl)-*N*-methyl methacrylamide (**4a**) and oxadiazole (**5**) were chosen as our test substrates (Scheme 2). After initial survey of reaction conditions, we were pleased to find that the racemic products **6a** and **10a** can be produced in 84% overall yield by heating a THF solution of **4a** and **5** in the presence of $Pd(OAc)_2$ (10 mol %), dppp (**L1**, 20 mol %), and Cs_2CO_3 (3.0 equiv) at 80 °C. Chiral ligands were next screened under these conditions utilizing the d.r. value of the dimers as an indicator of the enantioselectivity. The ligands producing the dimers with d.r. < 2 were not considered further since it implied that the ee_{dimer} of **6a** would be lower than 86.6%. Of note, the PHOX ligand **L2**,[19] the best performer in our previous studies involving aryltriflates as electrophilic partners,[17a] was completely ineffective. Three ligands, (*S*)-SEGPHOS **L14**, (*R*)-C3-TUNEPHOS **L15** and (*S*)-DIFLUORPHOS **L16**,[20] stood out from this screening. Further fine-tuning of the reaction conditions using these ligands indicated that $PdCl_2(MeCN)_2$ was a better palladium source than $Pd(OAc)_2$ at a lower catalyst loading (5 mol%) and that adding Ag_3PO_4 increased significantly the diastereoselectivity, hence the enantioselectivity, of this reaction. The role of the silver salt is likely due to its ability to abstract iodide from the palladium(II) intermediate leading to the 16-electron cationic Pd(II) species. This would allow the coordination of the tethered alkene to the metal center without interrupting the chelating property of the bidentate ligand, hence the higher intrinsic *ee* of the reaction.[21] Under optimized conditions (conditions iii with **L16**, Scheme 2), the reaction of **4a** with **5** afforded (*S*,*S*)-**6a** (99% *ee*) and (*S*,*R*)-**10a** in the isolated yields of 82% and 18% (4.4:1 d.r.), respectively.

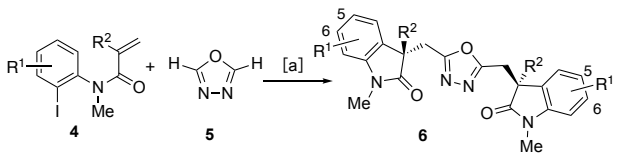
This domino process involving generation of the stereocenter, attachment of linker via C-H functionalization[22]



Scheme 2. Catalytic double enantioselective carbopalladation/direct intermolecular C-H functionalization. Reaction conditions: i) **4a** (0.25 mmol), **5** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.02 mmol), Cs_2CO_3 (0.3 mmol), THF, 80 °C. ii) **4a** (0.25 mmol), **5** (0.1 mmol), $PdCl_2(MeCN)_2$ (0.005 mmol), ligand (0.01 mmol), Cs_2CO_3 (0.3 mmol), THF, 80 °C. iii) conditions ii) + Ag_3PO_4 (0.1 mmol). Yields correspond to the purified products. The d.r. was determined by ^{1}H NMR spectrum of the crude product. The *ee* was determined by SFC using chiral stationary phase (see SI for details).

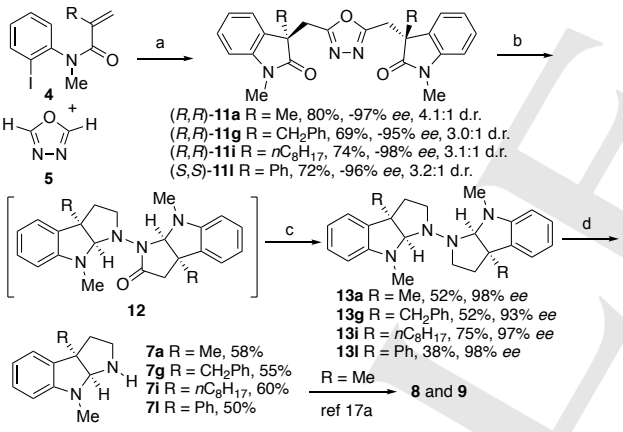
and *ee* enhancement via dimerization in one-pot was applicable to a wide range of substrates (Table 1). On the aniline part, electron-donating (**6b**) or electron-withdrawing (**6c**-**6f**) substituents located at different positions of the phenyl ring were tolerated affording homodimers in excellent yields and *ee*. High efficiency and selectivity was also observed with acetanilides bearing an alkyl group (linear, branched and functionalized) on the α-position of the double bond (**6a**-**6k**). For the substrates with the aryl substituent on the same position, the reaction has to be performed in MeCN under otherwise identical conditions. Bis-oxindoles **6l**-**6r** bearing an aromatic substituent with different electronic properties at C3 position were prepared with high efficiency and excellent enantioselectivities. The aryl chloride and aryl bromide were compatible to the present conditions providing therefore oxindoles with a handle for further functionalization. The absolute configuration of **6l** (*R*,*R*) was determined by X-ray crystallographic analysis and that of the other homodimers was assigned accordingly.[23]

Table 1. Scope of the double enantioselective carbopalladation/C-H functionalization



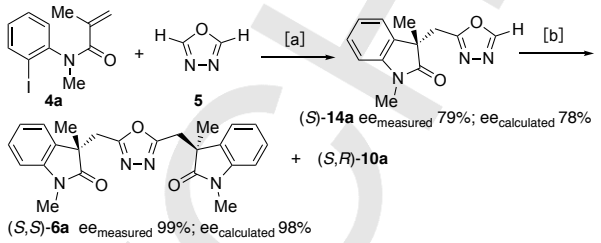
Entry	R^1	R^2	Product	Yield [%]	*ee* [%]	d.r.
1	5-OMe	Me	**6b**	84	99	5.7:1
2	5-Cl	Me	**6c**	75	98	3.8:1
3	5-Br	Me	**6d**	82	99	4.5:1
4	5-CN	Me	**6e**	80	95	4.5:1
5	6-Cl	Me	**6f**	76	99	4.9:1
6	H	Bn	**6g**	79	98	4.0:1
7	H	*i*Pr	**6h**	79	98	6.5:1
8	H	nC_8H_{17}	**6i**	74	95	3.1:1
9	H	CH_2OMe	**6j**	73	97	3.0:1
10	H	CH_2OAc	**6k**	70	98	5.0:1
11[b]	H	Ph	**6l**	69	96	3.6:1
12[b]	H	4-MeC_6H_4	**6m**	74	96	4.0:1
13[b]	H	4-$MeOC_6H_4$	**6n**	72	96	4.5:1
14[b]	H	4-FC_6H_4	**6o**	77	98	4.5:1
15[b]	H	4-PhC_6H_4	**6p**	70	97	4.1:1
16[b]	H	3-ClC_6H_4	**6q**	79	96	4.5:1
17[b]	H	2-Naphthyl	**6r**	52	96	5.0:1

[a] Standard conditions: **4a** (0.25 mmol), **5** (0.1 mmo), $PdCl_2(MeCN)_2$ (0.005 mmol), (*S*)-**L16** (0.01 mmol), Cs_2CO_3 (0.3 mmol), Ag_3PO_4 (0.1 mmol), THF (*c* 0.05 M), 80 °C, 24-72 h. [b] in MeCN at 120 °C under otherwise standard conditions. The d.r. was determined by ^1H NMR spectrum of the crude product. The *ee* was determined by SFC using chiral stationary phase (see SI for details).



Scheme 3. [a] **4** (0.25 mmol), **5** (0.1 mmol), $PdCl_2(MeCN)_2$ (0.005 mmol), (*R*)-**L16** (0.01 mmol), Ag_3PO_4 (0.1 mmol), Cs_2CO_3 (0.3 mmol), THF or MeCN (*c* 0.05 M), 80 °C, 24-72 h. [b] $LiAlH_4$, THF, 0 °C to reflux. [c] BH_3•Me_2S, Et_2O, 0 °C to RT. [d] Raney Ni, EtOH, H_2, 1 atm, 90 °C.

The same reaction between **4** and **5** using (*R*)-**L16** as ligand under otherwise identical conditions afforded (*R*,*R*)-**11**, an antipode of **6**, in high yields with excellent enantioselectivities (Scheme 3). Having demonstrated the validity of our approach, the transformation of these homodimers was investigated. The symmetric nature of oxadiazole and its vicinity with the amide function of the oxindole prompted us to examine the possibility of transforming **11** into a monomer with increased molecular complexity. It was found that reduction of bis-oxindoles **11** with $LiAlH_4$ afforded **12** which, without purification, was further reduced to C_2-symmetric bis-pyrroloindolines **13** without loss of the stereochemical integrity. Cleavage of the N-N bond of the hydrazine (Raney Ni, H_2) afforded two molecules of pyrroloindolines **7**. It is worth noting that only three molecules of water were formed as by-product per generation of two molecules of the target **7** from the dimer **11**. Compound (*R*,*R*)-**7a** has previously been converted to physostigmine (**8**) and esermethole (**9**)[17a]



Scheme 4 [a] **4a** (0.1 mmol), **5** (0.1 mmol), $PdCl_2(MeCN)_2$ (0.005 mmol), (*S*)-**L16** (0.01 mmol), Ag_3PO_4 (0.1 mmol), Cs_2CO_3 (0.15 mmol), THF (*c* 0.05 M), 80 °C, 2 h. [b] **14a** (0.1 mmol), **4a** (0.1 mmol), standard conditions.

The above domino process raised an interesting question regarding the second stereocenter-generating step: Was it substrate- or catalyst-controlled? If both were operating, was it a matched or a mismatched case?[24] To understand the reaction course, following control experiments were performed. Firstly, the monomer **14a** was prepared by reaction of **4a** with oxadiazole (**5**, 1.0 equiv) in the presence of (*S*)-**L16** under optimized conditions. The isolated monomer (*S*)-**14a** was allowed to react again with **4a** to produce the dimers (*S*,*S*)-**6a** and (*S*,*R*)-**10a**. The measured *ee* of monomer (*S*)-**14a** (78%) and dimer (*S*,*S*)-**6a** (*ee* 99%) matched well with the *ee* calculated from the d.r. (4.4/1) of the (*S*,*S*)-**6a** vs (*S*,*R*)-**10a**. Monitoring the formation of **6b-c** and **6f** bearing substituents with different electronic natures led to the same observation (see SI for data). Secondly, monitoring the reaction progress indicated that the *ee* of **6a** and **14a** remained constant as the reaction progressed (Table 2). Most importantly, reaction of the monomer (*S*)-**14a** (*ee* 78%) with **4a** in the presence of (*R*)-**L16** under standard conditions afforded racemic **6a** and **10a** with a d.r. of 1:4.1, which, within experimental error, was in agreement with our algebraic expression.[25] The results of these control experiments indicated clearly that the conversion of monomer **14** to dimer **6** was likely catalyst-controlled and that the easily measurable d.r. was indeed an excellent indicator for the enantioselectivity of the reaction.

Table 2. Evolution of *ee* of monomer **14a** and dimer **6a** vs reaction time

Entry	Time (h)	d.r.	**14a** (yield, *ee*)	**6a** (yield, *ee*)
1	1	4.2:1	69%, 78.5%	8.5%, 99.2%
2	3	4.2:1	79%, 78.5%	16%, 99.0%
3	6	4.2:1	77%, 78.0%	22%, 98.7%
4	10	4.2:1	30%, 78.0%	69%, 99.0%
5	22	4.2:1	0%, —	100%, 98.9%

In summary, we demonstrated that combining an enantioselective reaction with a dimerization is an efficient way to create chiral molecules with high enantiopurity. The salient features of the present work included: a) the linker was connected to the prochiral function via C-H functionalization; b) part of the linker was permanently incorporated into the structure of the monomeric target product rendering the introduction of the linker non-redundant; c) the *ee* of the product was uniformly high; d) the enantiopurity of the product can be estimated with

precision from the diastereomeric ratio (d.r.) of the dimers. Since the d.r. value is easily determined from the ^{1}H NMR spectrum of the crude product, it greatly accelerates the process of the condition optimization, especially in the initial stage of the ligand screening.[26] Further application of this approach to the reactions whose enantioselective versions are still difficultly achievable is underway.

Acknowledgements

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Keywords: Asymmetric synthesis • homogeneous catalyst • C-H activation • Horeau duplication principle • oxindole

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Synthetic Method

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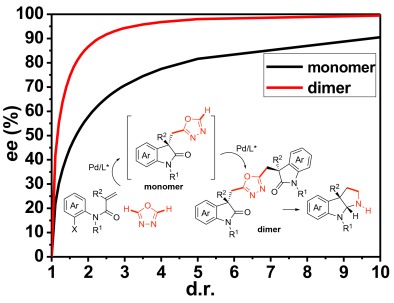
Catalytic Enantioselective Double Carbopalladation/C-H Functionalization with Statistical Amplification of Product Enantiopurity: A Convertible Linker Approach



A new dimension of Horeau duplication principle *Palladium-catalyzed reaction of N-(2-iodophenyl)-N-methyl methacrylamide derivatives with oxadiazole afforded homodimers in good yields with excellent enantiomeric excesses (ee). The dimer was subsequently converted to structurally elaborated monomer in which the linker (oxadiazole) was incorporated into the target product.*