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Authors: Xu Bao, Qian Wang, and Jieping Zhu

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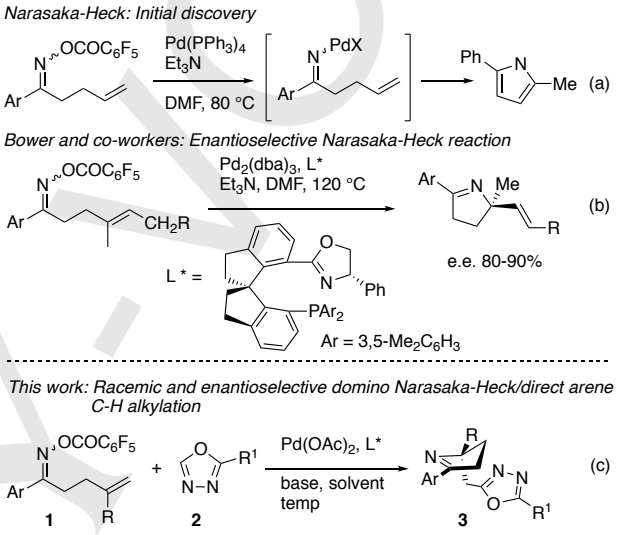
Palladium-Catalyzed Enantioselective Narasaka-Heck/Direct C-H Alkylation of Arene: Iminoarylation of Alkene**

Xu Bao, Qian Wang, Jieping Zhu*

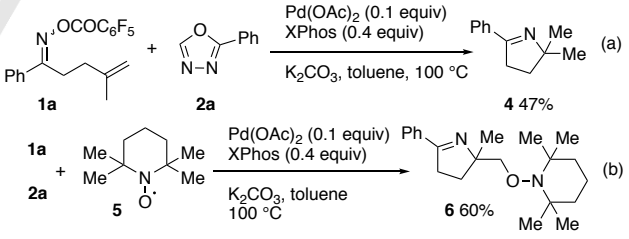
Abstract: *Palladium-catalyzed reaction of γ,δ-unsaturated oxime esters with oxadiazoles afforded dihydropyrroles in good to excellent yields via an intramolecular iminopalladation/ intermolecular direct heteroarene C-H alkylation cascade. This unprecedented iminoarylation of alkene was subsequently realized in an enantioselective manner in the presence of a chiral bidentate phosphine ligand (Synphos).*

Narasaka and co-workers reported in 1999 a palladium-catalyzed cyclization of γ,δ-unsaturated oxime esters for the synthesis of pyrroles (Scheme 1a).[1] The reaction was initiated by oxidative addition of acyloxime to Pd(0) leading to iminopalladium(II) complex which then underwent an intramolecular iminopalladation with the tethered double bond. In this process, nitrogen atom acted in the initiation step as an electrophilic centre in sharp contrast to most of the other palladium-catalyzed amination reactions wherein the nitrogen atom acted as a nucleophile.[2] Since this pioneer report, various N-heterocycles including pyridine, [3] azaazulene,[4] imidazole,[5] aziridine,[6] indole,[7] phenanthridine,[8] isoquinoline,[8,9] dihydropyrrole, [10,11] have been synthesized by combining the iminopalladation process with Heck, Suzuki-Miyuara, intramolecular C-H arylation and chlorination reactions. Extensive investigation of Bower and coworkers demonstrated that, by tuning the nature of the ligand and the substrate structure, it was possible to generate dihydropyrroles/perhydroindoles with concurrent generation of a secondary or a tertiary stereogenic center.[11] This is of significant importance in view of the wide spread presence of chiral nitrogen containing heterocycles in natural products and drugs.[12] Very recently, Bower has developed the first efficient catalytic asymmetric Narasaka-Heck reaction leading to 2,5,5-trisubstituted dihydropyrrole in good to excellent enantioselectivities (Scheme 1b).[11b,13]

Our group has been interested in developing domino process initiated by carbopalladation reaction.[14] While enantioselective Heck reaction has been well documented over the years,[15] the development of enantioselective carbopalladation/nucleophilic trapping of the transient C(sp^3)-Pd species is known to be challenging.[16-19] Indeed, the presence of nucleophilic species, whether neutral or ionic, can potentially coordinate to Pd, modifying consequently the asymmetric environment created by chiral ligand. We report herein the first examples of domino Narasaka-Heck iminopalladation/direct heteroarene C-H alkylation sequence as well as its catalytic enantioselective variant for the synthesis of functionalized dihydropyrroles (Scheme 1c).



Scheme 1. Evolution of Narasaka-Heck reaction: from heteroarenes to chiral heterocycles.



Scheme 2. Narasaka-Heck cyclization: a competitive radical pathway.

We began by investigating the reaction of 4-methyl-1-phenylpent-4-en-1-one *O*-(pentafluorobenzoyl ester) oxime (**1a**) with 2-phenyl-1,3,4-oxadiazole (**2a**). The projected domino reaction involved a sequence of oxidative addition of oxime ester to Pd(0), intramolecular iminopalladation and direct heteroarene C-H alkylation with the transient σ-C(sp^3)-Pd complex. The results of the initial experiments were disappointing. For example, performing the reaction of **1a** and **2a** in the presence of $Pd(OAc)_2$ and XPhos in toluene afforded 2,2-dimethyl-5-phenyl-3,4-dihydro-*2H*-pyrrole (**4**) in 47% yield (Scheme 2a). When the same reaction was carried out in the presence of TEMPO (**5**), the radical trapping product **6** was isolated in 60% yield (Scheme 2b). These results clearly indicated that the radical mechanism could be operating under this Pd-catalyzed reaction.[11f] Fortunately, it was found that

[*] Dr. X. Bao, Dr. Q. Wang, Prof. Dr. J. Zhu
Laboratory of Synthesis and Natural Products
Institute of Chemical Sciences and Engineering
Ecole Polytechnique Fédérale de Lausanne
EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne (Switzerland)
E-mail: jieping.zhu@epfl.ch
Homepage: http://lspn.epfl.ch
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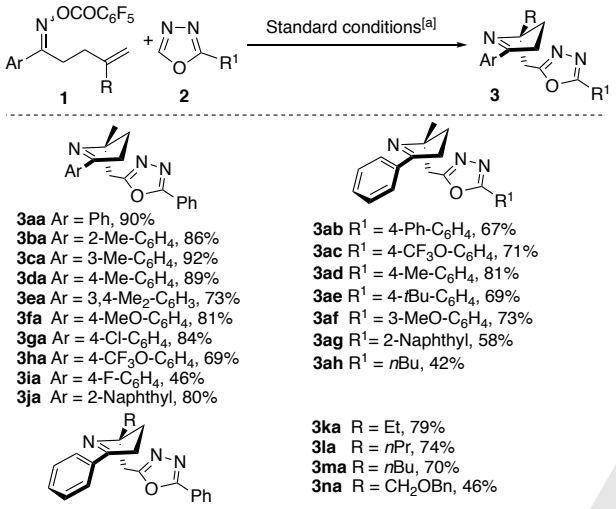
solvent can effectively divert the reaction mechanism. Performing the reaction of **1a** and **2a** in DMF under otherwise identical conditions afforded the coupling product **3aa** in 30% yield together with the hydrolysis product 4-methyl-1-phenylpent-4-en-1-one. Systematic survey of reaction parameters varying the nature of ligands, the solvents, the bases and the additives allowed us to identify following optimum conditions: $Pd(OAc)_2$ (0.1 equiv), (±)-BINAP (0.2 equiv), *i*Pr_2NEt (4.0 equiv), Cs_2CO_3 (3.0 equiv), DMSO, 120 °C (See Supporting Information for detailed survey of reaction conditions). Under these conditions, reaction of **1a** and **2a** afforded compound **3aa** in 90% isolated yield (Scheme 3).



Scheme 3. Substrate scope. [a] Standard conditions: **1a** (0.2 mmol), **2a** (0.10 mmol), $Pd(OAc)_2$ (0.1 equiv), (±)-BINAP (0.2 equiv), Cs_2CO_3 (0.3 mmol), *i*Pr_2NEt (0.4 mmol), DMSO (1.0 mL), 120 °C, 8 h.

This novel iminopalladation/direct heteroarene C-H alkylation protocol was applicable to a large set of substrates. As shown in Scheme 3, substituents regardless of their electronic nature and positions on the aryl group (Ar) of the oxime ester were well tolerated (**3aa**-**3ja**). The same was true for the C2 substituents of the oxadiazole (**3ab**-**3ag**) although the 2-butyl oxadiazole afforded the coupling product **3ah** in diminished yield. Of note, the aryl chloride was stable under our reaction conditions and chlorinated product **3ga** was isolated in excellent yield. Alkyl groups (Me, Et, *n*Pr, *n*Bu) including functionalized one (CH_2OBn) attached to the double bond were well tolerated (**3ka**-**3na**, Scheme 3).

We next turned our attention to the enantioselective version of the Narasak-Heck/direct cross-coupling process.[20] Using (*R*)-BINAP under otherwise standard conditions, reaction of **1a** and **2a** afforded indeed **3aa** in 57% yield with an encouraging e.r. of 82.5:17.5. Conditions were therefore further optimized by varying the Pd sources, ligands, bases and solvents (*cf* Supporting Information for details) and following observations were made: a) Potassium carbonate and cesium carbonate were the bases of choice and the former was used for the subsequent studies. Tertiary amine bases (Et_3N, *i*Pr_2NEt, Et_2NPh, DBU, DABCO, MTBD) alone or in combination with K_2CO_3 reduced the reaction efficiency. Tetramethylguanidine (TMG), the base of significant importance in our previous enantioselective carbopalladation/CH-functionalization,[18] inhibited completely the occurrence of the desired process; b) Among the various chiral ligands screened, biaryl-based bidentate phosphine ligands such as BINAP, Segphos and Synphos provided good enantioselectivities, with (*S*)-Synphos[21] being the best in terms of both yield and e.r. of the product (Figure 1, see Supporting Information for complete list of ligands screened). To exploit the steric and electronic effects on the reaction efficiency, Synphos analogues (**L7** and **L8**) and (*S*)-Solphos,[22] an aza analogue of (*S*)-Synphos, were synthesized. However, none of them provided product **3aa** with better e.r. than the Synphos itself. The reaction using *t*Bu-PHOX[23] as a supporting ligand afforded only a trace amount of desired product; c) DMSO was the solvent of choice among those screened (DMF, MeCN). Overall, under optimized conditions [**1a** (0.2 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), (*S*)-Synphos (0.2 equiv), K_2CO_3 (3.0 equiv), DMSO, 100 °C], reaction of **1a** and **2a** afforded **3aa** in 90% yield with an e.r. of 92:8.

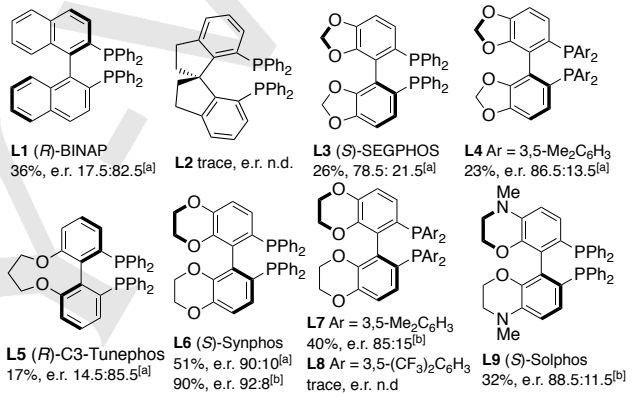


Figure 1. Chiral biphosphine ligands screened for the enantioselective synthesis of **3aa**. [a] Standard conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $Pd(OAc)_2$ (0.025 equiv), Ligand (0.05 equiv), K_2CO_3 (0.2 mmol), DMF (1.0 mL), 100 °C, 8 h; [b] **1a** (0.2 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), Ligand (0.2 equiv), K_2CO_3 (0.3 mmol), DMSO (1.0 mL), 100 °C, 8 h.

The scope of this enantioselective domino process was next investigated (Scheme 4). In general, the conditions were applicable to oxime esters having different aryl and alkyl substituents (Ar and R groups in **1**). Oxadiazoles with diverse substituents at C2 were also tolerated. In most cases, the 2,5,5-trisubstituted dihydropyrroles **3** were isolated in good yields with good to high enantioselectivities. The (*S*)-absolute configuration of **3ag** was determined by X-ray crystallographic analysis.[24] Consequently, that of the other dihydropyrroles was assigned accordingly. Unfortunately, other heterocycles such as benzoxazole and benzothiazole failed to participate in this reaction.[25]

A possible reaction pathway is depicted in Scheme 5. Oxidative addition of oxime ester to Pd(0) would afford intermediate **A** that would most probably exist as a cationic species as demonstrated previously by Bower and co-workers.[11] Coordination of the electrophilic cation Pd(II) complex to the tethered double bond followed by intramolecular *syn*-iminopalladation would afford dihydropyrrole with concurrent generation of the chiral quaternary stereocenter and the σ-C(sp^3)-Pd(II) species. In

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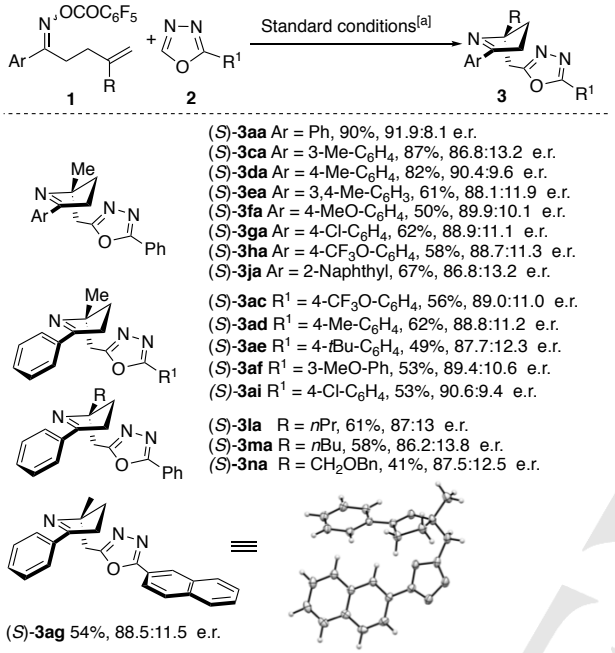
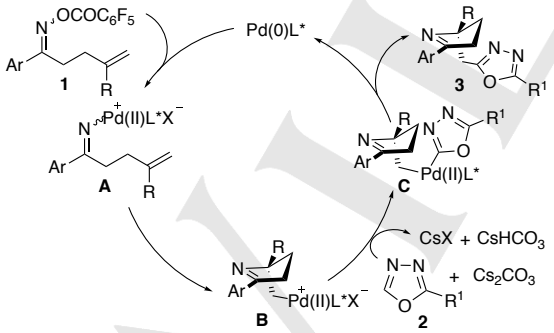
parallel, deprotonation of oxadiazole's C5-H with Cs_2CO_3 or K_2CO_3 would generate the oxadiazole anion, which, upon transmetallation with **B**, would afford **C**. Reductive elimination from the latter would then furnish the observed product **3**. In line with the classic enantioselective Heck reaction, we assumed that the cationic Pd(II) intermediate **A** is of utmost importance to the desired asymmetric induction. Since this species has a free coordination site available for the alkene, the bidentate ligand can therefore remain chelated to Pd creating therefore the chiral environment needed for the efficient chirality transfer.[15]

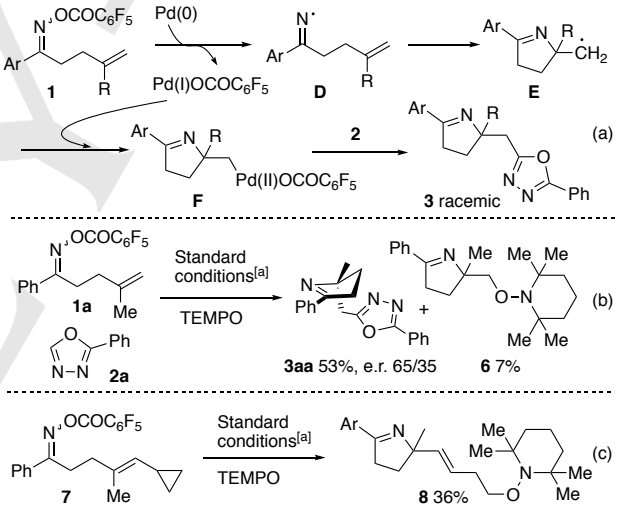


Scheme 4. Scope of the enantioselective iminopalladation/direct C-H functionalization. [a] **1a** (0.2 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), (*S*)-Synphos (0.2 equiv), K_2CO_3 (0.3 mmol), DMSO (1.0 mL), 100 °C, 8 h; yield referred to isolated product; e.r. was determined by SFC on chiral stationary phase. *Abbrev*. Synphos = [(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′ diyl]bis(diphenylphosphine).



Scheme 5. Possible reaction pathway.

The development of enantioselective Narasaka-Heck type reactions is known to be highly challenging due to the mechanistic complexity. Indeed, if the reaction were initiated by cyclization of the iminyl radical **D** to the pendant double bond, then the intermediate **E** generated would be racemic. In the absence of good hydrogen donor, the radical **E** could recombine with the Pd(I) species to generate the Pd(II) complex **F** which could then alkylate the oxadiazole leading to the racemic product **3** (Scheme 6a).[26] To probe this mechanistic possibility, the reaction of **1a** and **2a** was performed in the presence of TEMPO under otherwise identical conditions. As it is seen (Scheme 6b), the reaction afforded indeed the radical trapping product **6** (7% yield) together with compound **3aa** in 53% yield with an e.r. of 65/35. Since the presence of TEMPO could potentially provoke the radical process,[27] the diminished enantioselectivity is therefore understandable. Although the formation of **6** was not a definitive evidence to support the radical mechanism in its absence, the fact that **3aa** was still produced was highly indicative of the occurrence of the mechanism depicted in Scheme 6a and that the radical recombination of **E** with Pd(I)X was kinetically competitive with the TEMPO trapping process. On the other hand, treatment of **7** under standard conditions, afforded **8** in 36% yield, providing further evidence of the radical mechanism (Scheme 6c). The concurrent occurrence of the radical pathway would obviously render the development of highly enantioseletive Narasaka-Heck type reaction extremely difficult.



Scheme 6. Possible competitive radical mechanism and results of control experiments. [a] **1a** (0.2 mmol), **2a** (0.1 mmol), TEMPO (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), (*S*)-Synphos (0.2 equiv), K_2CO_3 (0.3 mmol), DMSO (1.0 mL), 100 °C, 8 h.

In summary, we have developed the first examples of palladium-catalyzed Narasaka-Heck iminopalladation/direct arene C-H alkylation cascade. The domino process produced 2,5,5-trisubstituted dihydropyrroles via formation of one $N(sp^2)$-$C(sp^3)$ bond and one $C(sp^3)$-$C(sp^2)$ bond. One quaternary stereocenter was generated in this process and an enantioselective variant was developed leading to the dihydropyrroles in good yields with good to high enantioselectivities. The observed solvent-dependant mechanistic dichotomous (SET vs two electron process) and possible concurrent occurrence of these two mechanisms in a given set of conditions is unique in Pd-catalyzed transformations which shed light on the difficulties associated with the development of enantioselective Narasaka-Heck reaction.

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Layout 1:

Synthetic Method

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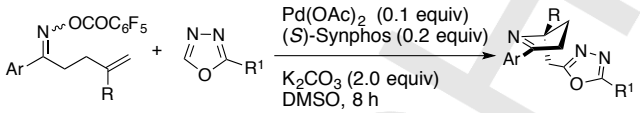
Palladium-Catalyzed Enantioselective Narasaka-Heck/Direct C-H Alkylation of Arene: Iminoarylation of Alkene



Minimising Radical Process. *Palladium-catalyzed reaction of γ,δ-unsaturated oxime esters wit oxadiazoles afforded enantioenriched dihydropyrroles in excellent yields via an asymmetri iminopalladation/direct arene C-H alkylation cascade.*