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Palladium/GF-Phos-catalyzed asymmetric carbenylative amination to access chiral pyrrolidines and piperidines†

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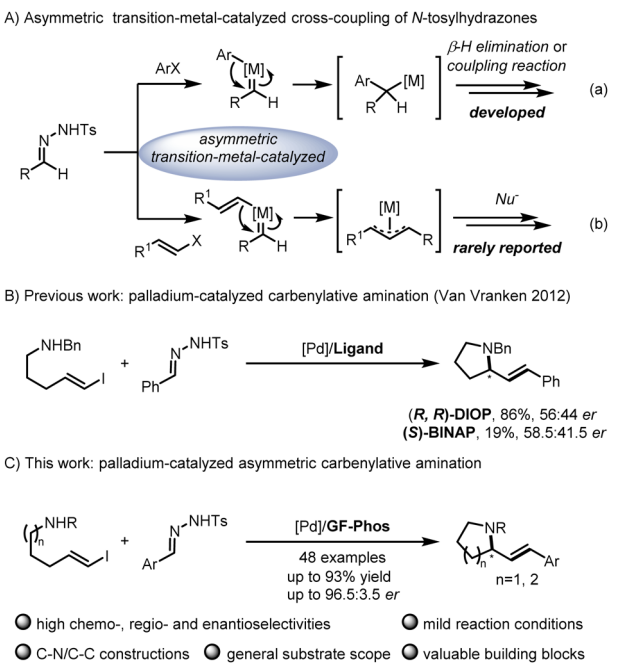
The cross-coupling of *N*-tosylhydrazones has emerged as a powerful method for the construction of structurally diverse molecules, but the development of catalytic enantioselective versions still poses considerable challenges and only very limited examples have been reported. We herein report an asymmetric palladium/GF-Phos-catalyzed carbenylative amination reaction of *N*-tosylhydrazones and (*E*)-vinyl iodides pendent with amine, which allows facile access to a range of chiral pyrrolidines and piperidines in good yields (45–93%) with up to 96.5 : 3.5 *er*. Moreover, mild conditions, general substrate scope, scaled-up preparation, as well as the efficient synthesis of natural product (−)-norruspoline are practical features of this method.

N-tosylhydrazones, readily prepared from aldehydes or ketones, served as a safe source of carbene precursors and have attracted much attention of chemists.[1] *N*-tosylhydrazone-mediated applications have been continuously developed, such as cyclopropanation or cyclopropenation, X–H insertion, ylide formation, cycloaddition, aza-Wacker-type cyclization, asymmetric allylic substitution, *etc.*[2] Among them, transition-metal-catalyzed cross-coupling is one of the powerful protocols for C–X or C=C bond formation in organic synthesis involving versatile intermediates, of which *in situ* generation of diazo compounds and carbene migratory insertion are considered key steps.[3–5] Over the past decades, considerable progress has been made in the asymmetric cross-coupling reactions of *N*-tosylhydrazones with various coupling partners, including cyclobutanols, terminal alkynes, silacyclobutanes and so on.[4] Relatively, only a few examples focus on the cross-coupling reactions of aryl halides with *N*-tosylhydrazones involving benzyl metal intermediates [Scheme 1A, eqn. (a)].[6] For example, Gu,[6a] Wu,[6b] Lassaletta[6c] and coworkers have developed a palladium-catalyzed asymmetric synthesis of axial chiral compounds from aryl bromides and *N*-tosylhydrazones, ending with β-H elimination. Very recently, we realized palladium/GF-Phos catalyzed asymmetric three component cross-coupling reactions of aryl halides, *N*-tosylhydrazones, with terminal alkynes.[6f] In contrast, much less progress has been made in *N*-tosylhydrazone-based carbenylative insertions from vinyl halides, which would generate a π-allylic metal intermediate followed by nucleophile attack, providing a unique approach for building C–X bonds, especially for *N*-heterocyclic compounds [Scheme 1A, eqn. (b)].[7] *N*-heterocycles are important structural motifs for the development of various types of valuable chemicals and materials.[8] Importantly, optically active 2-substituted pyrrolidine and piperidine derivatives are privileged scaffolds in many natural products and pharmaceuticals with a wide range



Scheme 1 Asymmetric transition-metal-catalyzed carbenylative cross-coupling reactions.

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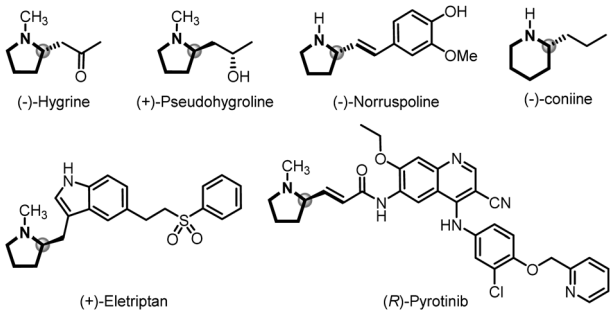


Fig. 1 Selected natural products and pharmaceuticals containing chiral 2-substituted pyrrolidine and piperidine units.

of biological activities,[9] as well as the backbone of organocatalysts in asymmetric catalysis (Fig. 1).[10]

Notably, Van Vranken and coworkers reported an elegant palladium-catalyzed carbenylative amination reaction of *N*-tosylhydrazones and (*E*)-vinyl iodides pendent with amine, providing facile access to pyrrolidine and piperidine ring systems that are common to alkaloid natural products (Scheme 1B).[11] Unfortunately, only up to 58.5 : 41.5 *er* was obtained after they made a lot of efforts to screen a series of chiral phosphine ligands, indicating that this asymmetric reaction indeed poses considerable challenges in addition to competitive side reactions such as the dimerization of vinyl iodides,[12] the formation of diene *via* the palladatropic rearrangement/β-H elimination or allene *via* β-H elimination from C_{sp^2},[13] and the π-allylpalladium intermediate trapped by the byproduct sulfinic acid salt.[14] Given the significance of chiral pyrrolidines and piperidines as core structures in alkaloid natural products, the development of an asymmetric version of this elegant carbenylative amination reaction is highly desirable. In recent years, our group has developed a series of chiral sulfinamide phosphine ligands (so-called **Sadphos**), which showed unique potential in asymmetric transition-metal catalysis,[6f,15] so we wondered whether Sadphos could address this challenging asymmetric carbenylative amination reaction (Scheme 1C).

Initially, our study began with (*E*)-vinyl iodide **1a** and *N*-tosylhydrazone **2a** in the presence of $Pd_2(dba)_3$, *t*-BuOLi, Et_3N, and triethylbenzylammonium chloride (TEBAC) in THF at 30 °C. A series of commercially available chiral ligands were first screened (Fig. 2). Only (*R*, *R*)-DIOP (**L1**), (*R*)-DTBM-SegPhos (**L3**) and (*R*)-MOP (**L4**) provided the desired product **3aa** with poor enantioselectivity and other ligands such as (*R*, *R*)-Ph-BPE (**L2**), (*R*, *S*)-Josiphos (**L5**) and (*S*, *S*)-^{i}Pr-FOXAP (**L6**) showed low reactivity. We next turned to systematically investigate Sadphos, such as Wei-Phos,[16] Xiao-Phos,[15d,17] Ming-Phos,[15a,18] Xu-Phos,[15b,19] Xiang-Phos[20] and PC-Phos[15c,21] (Fig. 2). To our delight, **PC1** delivered **3aa** in 32% yield and 85.5 : 14.5 *er*. Inspired by this result, we further screened **PC2–PC5** which vary in the substituent of phenyl, but unfortunately none of them showed better results. Surprisingly, the reactivity of this reaction could be greatly improved with our recently developed GF-Phos **GF1**, delivering 71% yield. When steric hindered *tert*-butyl groups were introduced on the phenyl group (**GF2**), the product **3aa** was

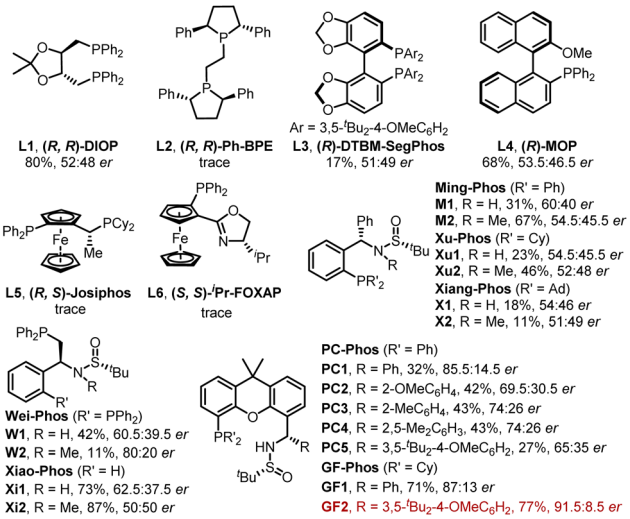
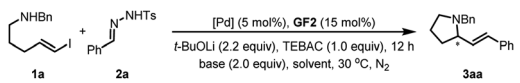


Fig. 2 Screened chiral ligands.

obtained in 77% yield with 91.5 : 8.5 *er*. After screening different palladium catalysts and solvents (Table 1, entries 1–10), the *er* value has been slightly increased. Additionally, lowering reaction temperature led to an increase in enantioselectivity but a decrease in yield (Table 1, entry 11).

We also found that, besides *t*-BuOLi, there was little effect on the yield or enantioselectivity by changing another base. The

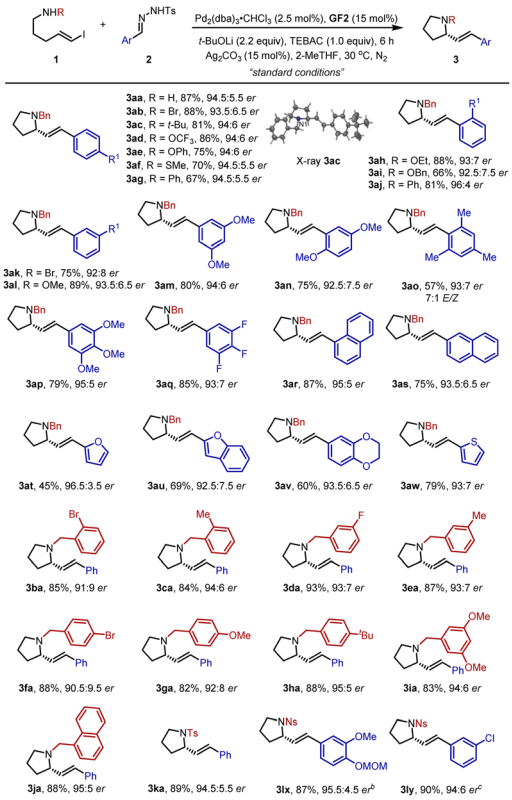
Table 1 Optimization of reaction conditions[a]



Entry	[Pd]	Base	Solvent	Yield[b] (%)	*er*[c]
1	$Pd_2(dba)_3$	Et_3N	THF	77	91.5 : 8.5
2	$Pd(acac)_2$	Et_3N	THF	89	86.5 : 13.5
3	$Pd(OAc)_2$	Et_3N	THF	82	88 : 15
4	$PdBr_2$	Et_3N	THF	78	88 : 12
5	$Pd_2(dba)_3 \cdot CHCl_3$	Et_3N	THF	75	92 : 8
6	$Pd_2(dba)_3 \cdot CHCl_3$	Et_3N	Toluene	23	92.5 : 7.5
7	$Pd_2(dba)_3 \cdot CHCl_3$	Et_3N	DMF	90	80 : 20
8	$Pd_2(dba)_3 \cdot CHCl_3$	Et_3N	MTBE	28	93 : 7
9	$Pd_2(dba)_3 \cdot CHCl_3$	Et_3N	1,4-Dioxane	38	88.5 : 11.5
10	$Pd_2(dba)_3 \cdot CHCl_3$	Et_3N	2-Me-THF	89	93 : 7
11[d]	$Pd_2(dba)_3 \cdot CHCl_3$	Et_3N	2-Me-THF	26	94.5 : 5.5
12	$Pd_2(dba)_3 \cdot CHCl_3$	DABCO	2-Me-THF	76	94 : 6
13	$Pd_2(dba)_3 \cdot CHCl_3$	Cs_2CO_3	2-Me-THF	93	92.5 : 7.5
14	$Pd_2(dba)_3 \cdot CHCl_3$	KOH	2-Me-THF	89	93 : 7
15	$Pd_2(dba)_3 \cdot CHCl_3$	None	2-Me-THF	83	93 : 7
16[e]	$Pd_2(dba)_3 \cdot CHCl_3$	None	2-Me-THF	69	88 : 12
17[f]	$Pd_2(dba)_3 \cdot CHCl_3$	None	2-Me-THF	81	94.5 : 5.5

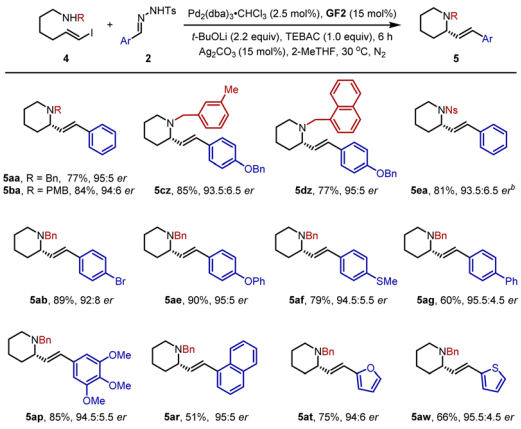
[a] Reaction conditions: **1a** (0.1 mmol), 2a (0.16 mmol), [Pd] (5 mol%), GF2 (15 mol%), t-BuOLi (2.2 equiv.), TEBAC (1.0 equiv.), base (2.0 equiv.) in 0.1 M solvent at 30 °C for 12 h. [b] Determined by GC analysis with *n*-tetradecane as an internal standard. [c] The *er* value was determined by chiral HPLC. [d] 15 °C for 12 h. [e] Without TEBAC. [f] 15 mol% Ag_2CO_3. THF = tetrahydrofuran. MTBE = *tert*-butyl methyl ether. DMF = *N*,*N*-dimethylformamide. DCE = 1,2-dichloroethane. DMSO = dimethyl sulfoxide.

Table 2 Scope for enantioselective formation of pyrrolidines[a]



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.48 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%). **GF2** (15 mol%), *t*-BuOLi (2.2 equiv.), TEBAC (1.0 equiv.), Ag_2CO_3 (15 mol%) in 0.1 M 2-MeTHF at 30 °C for 6 h. [b] 1.8 mmol scale, 24 h. [c] 2.0 mmol scale, 20 h.

Table 3 Scope for enantioselective formation of piperidines[a]

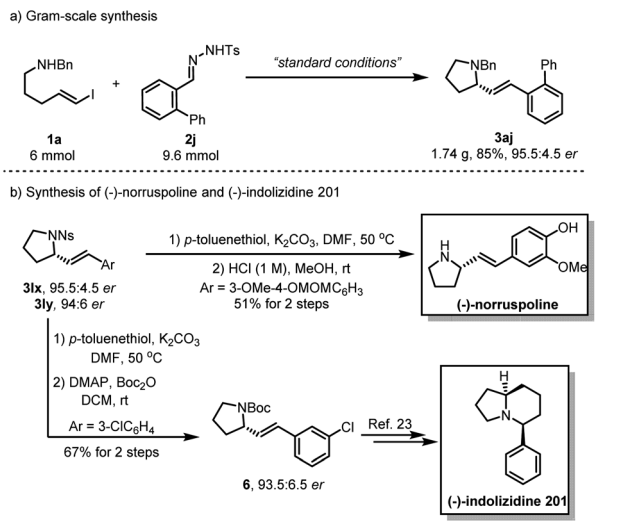


[a] Reaction conditions: **1** (0.3 mmol), **2** (0.48 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), **GF2** (15 mol%). *t*-BuOLi (2.2 equiv.), TEBAC (1.0 equiv.), Ag_2CO_3 (15 mol%) in 0.1 M 2-MeTHF at 30 °C for 6 h. [b] 12 h.

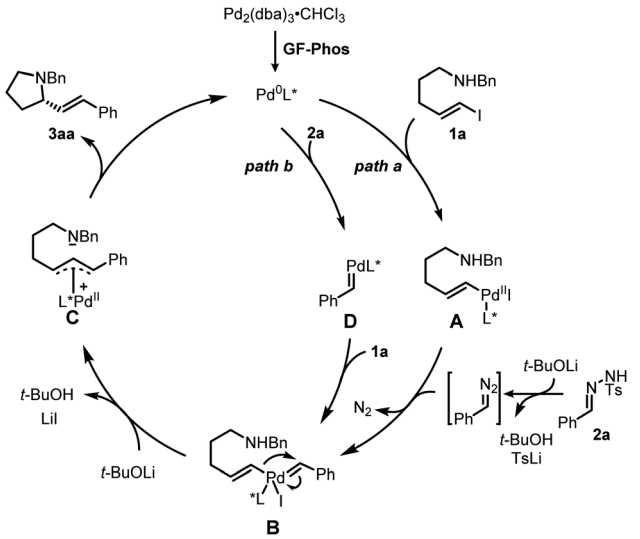
study was therefore continued without it (Table 1, entries 12–15). Moreover, in the absence of TEBAC, **3aa** was produced in only 69% yield and 88 : 12 *er*. TEBAC probably helps to increase the solubility of the anion of *N*-tosylhydrazones (Table 1, entry 16). Interestingly, we investigated a series of additives, and the results indicated that the addition of Ag_2CO_3 could further provide slightly higher enantioselectivity (94.5 : 5.5 *er*) (Table 1, entry 17, see the ESI for more details†).

The scope of the carbenylative amination reaction was then studied using the optimized reaction conditions (Table 2). A wide range of *N*-tosylhydrazones **2** bearing electron-withdrawing or donating groups at the *ortho*-, *meta*- or *para*-position of the phenyl ring were tested, giving the corresponding products **3aa–3aj** in moderate to good yields with 92.5 : 7.5–96 : 4 *er*. The absolute configuration of **3ac** was confirmed as *S* by single crystal X-ray diffraction analysis.[22] Multisubstituted phenyl and naphthyl groups were also well-tolerated (**3am**, **3an**, **3ap–3as**). It is note-worthy that the 2,4,6-trimethylphenyl-substituted substrate delivered **3ao** in 57% yield with 7/1 *E*/*Z* selectivity, probably due in part to the steric hindrance. Moreover, *N*-tosylhydrazones containing heterocycles reacted smoothly to furnish the expected products **3at–3aw**. Besides diverse substituted *N*-tosylhydrazones **2**, various kinds of vinyl iodide derivatives **1** with functional groups such as halides, methyl, *tert*-butyl, methoxy and 1-naphthyl at different positions on the phenyl ring also worked well and afforded **3ba–3ja** in good yields. Surprisingly, when the protective group on the nitrogen atom was replaced by a *p*-toluenesulfonyl or *p*-nitrophenylsulfonyl group, the corresponding cyclic products **3ka**, **3lx**, and **3ly** were successfully produced in high yields and enantioselectivities.

Subsequently, we further turned our efforts to the synthesis of piperidine derivatives. As shown in Table 3, the desired six-membered heterocycles **5aa–5dz** could be obtained efficiently in 77–85% yields with 93.5 : 6.5–95 : 5 *er* under standard conditions. Similarly, the *p*-nitrophenylsulfonyl group was also a compatible partner to give **5ea** in 81% yield with 93.5 : 6.5 *er*. In parallel, a variety of *N*-tosylhydrazones **2** mentioned above were studied, affording structurally diverse piperidines **5ab–5ar** smoothly. In addition, 2-furan- and thienyl-substituted *N*-



Scheme 2 Gram-scale synthesis and synthetic applications.



Scheme 3 Proposed catalytic cycle.

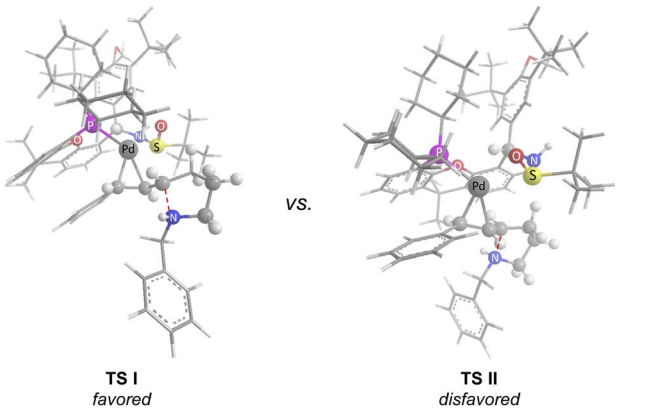


Fig. 3 Proposed chirality induction model.

tosylhydrazones were transformed into **5at** and **5aw** in good yields with high *er* values.

To evaluate the synthetic utility of this asymmetric carbenylative amination reaction, we carried out a gram–scale reaction under standard conditions, providing the product **3aj** in 85% yield with 95.5 : 4.5 *er* (Scheme 2a). Of note, a 2-step deprotection of **3lx** with *p*-toluenethiol/K_2CO_3 and HCl (1 M) enabled the synthesis of natural product (−)-norruspoline in 51% overall yield. Additionally, replacing the protecting group of **3ly** with the Boc group afforded **6** in 67% yield without the loss of enantioselectivity and it has been previously shown that **6** is a synthetic intermediate for the preparation of natural product (−)-indolizidine 201 (Scheme 2b).[23] A linear relationship was demonstrated by a nonlinear effect study on the *ee* value of **GF2** and product **3aa**, which implied that the catalytically active structure contains only a single chiral ligand. (please find more details in the ESI†).

Based on our study and previous work,[24] a catalytic cycle pathway to rationalize the synthesis of chiral pyrrolidines is illustrated in Scheme 3. First, the oxidative addition of vinyl iodide **1a** to a Pd^0/GF-Phos complex would generate vinyl Pd^{II} species **A**. In the presence of a base, *N*-tosylhydrazone **2a** *in situ* generated a diazo intermediate and formed palladium carbene **B** with vinyl Pd^{II} species **A**, followed by migratory insertion to generate the π-allylpalladium intermediate **C**, as displayed in path a. Alternatively, the reaction proceeds in a palladium carbene/oxidative addition sequence as in path b. Next, the nucleophilic attack of the nitrogen atom on π-allylpalladium delivered product **3aa** and regenerated the Pd^0 complex, thus completing the entire catalytic cycle. In light of the structure of the chiral ligand **GF2** and the absolute configuration of product (*S*)-**3**, a chirality induction model for stereochemical induction was proposed (Fig. 3).

In conclusion, we have developed a palladium/GF-Phos catalyzed asymmetric carbenylative amination of (*E*)-vinyl iodides with *N*-tosylhydrazones *via* a carbene migratory insertion/Tsuji-Trost sequence to build C–N/C–C more efficiently. This catalytic system exhibits general functional group tolerance and enables rapid access to a variety of chiral 2-substituted pyrrolidines and piperidines in moderate to good yields with high chemo-, regio-, enantioselectivities under mild conditions. Our approach can be applied to the direct synthesis of significant natural product (−)-norruspoline and provides an alternative route for the formal synthesis of (−)-indolizidine 201.

Data availability

All experimental data and detailed experimental procedures are available in the ESI.†

Author contributions

Y. S. conducted the experiments and analysed the data. C. M. conducted the preparation of the starting materials. Z. L. and J. Z. directed the project. Y. S., Z. L. and J. Z. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

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