Communication

Intermolecular Palladium(0)-Catalyzed Atropo-enantioselective C–H Arylation of Heteroarenes

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Intermolecular Palladium(0)-Catalyzed Atropo-enantioselective C–H Arylation of Heteroarenes

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Supporting Information Placeholder

ABSTRACT: Atropisomeric (hetero)biaryls are motifs with increasing significance in ligands, natural products and biologically active molecules. The straightforward construction of the stereogenic axis by efficient C–H functionalization methods is extremely rare and challenging. An intermolecular and highly enantioselective C–H arylation of relevant heteroarenes providing an efficient access to atropisomeric (hetero)biaryls is reported. The use of a Pd(0) complex equipped with H_8-BINAPO as chiral ligand enables the direct functionalization of a broad range of 1,2,3-triazoles and pyrazoles in excellent yields and selectivities of up to 97.5:2.5 *er*. The method also allows for an atroposelective double C–H arylation for the construction of two stereogenic axes with >99.5:0.5 *er*.

Atropisomerism is the time-dependent chirality arising from an impediment of free rotation about an axis in a molecule. Such axially chiral molecules are an important source of stereoinduction in asymmetric catalysis,[1] as well abundantly found in natural products.[2] Recently, the use of atropisomeric (hetero)biaryl motifs with *ortho* substituents to lock biaryl bond rotation has garnered attention and is a current trend in drug discovery.[3] These molecules frequently display enhanced stereochemical recognition of biological targets compared to their achiral counterparts.[4] Representative examples of atropisomeric (hetero)biaryls in ligands (StackPHOS),[5] natural products (Rivularin D3)[6] and bioactive molecules (202W92,[7] BI22436[8]) are depicted in Figure 1A. Given the relevance of this motif, significant efforts have been dedicated to their asymmetric synthesis.[9] Catalytic approaches belong to four strategies: (i) enantioselective *de novo* synthesis of an aromatic ring,[10] (ii) central-to-axial chirality transfer,[11] (iii) locking a pre-existing axis,[12] and (iv) enantioselective formation of a (hetero)biaryl linkage. The asymmetric construction of the biaryl axis is straightforward in terms of retrosynthetic disconnection, but remains challenging in practice. The high steric demands of the substrates required to block rotation around the axis reduces their chemical reactivity. In this respect, the Suzuki–Miyaura coupling has achieved high levels of enantiocontrol and good reactivity.[13] However, the cross-coupling methodology requires the use and availability of two pre-functionalized substrates.

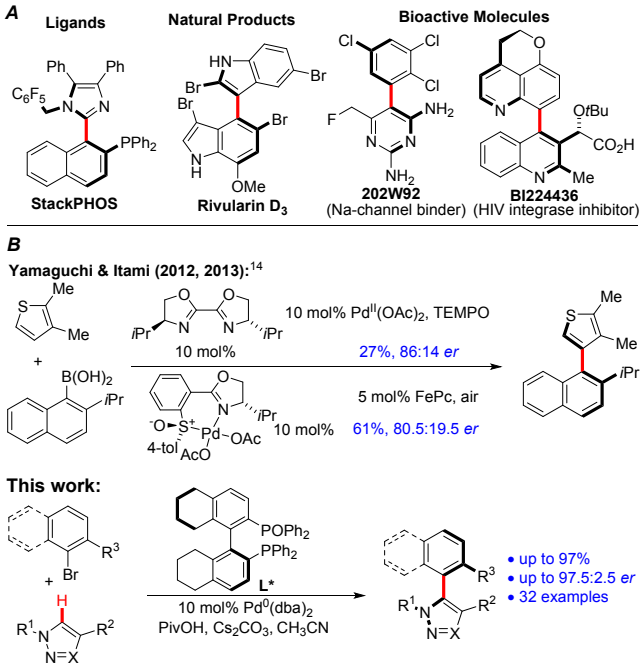
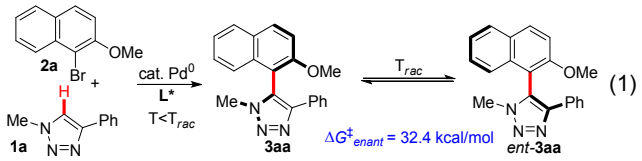


Figure 1. (A) Compounds with atropisomeric heterobiaryl C–C linkage. **(B)** Intermolecular atropo-enantioselective C–H functionalization approach.

Complementarily, the enantioselective direct C–H arylation of (hetero)arenes – while being more atom-efficient and direct – remains a very underdeveloped field. The underlying challenges become quickly apparent from the two reported cases proceeding both in modest yields and enantioselectivities (Figure 1, B). In 2012, Yamaguchi and Itami reported two examples of an oxidative Pd(II)-catalyzed coupling proceeding in 27% yield and 86:14 *er*.[14a] One year later, they reported another ligand and oxidant providing 61% yield and 80.5:19.5 *er* for the same substrate.[14b] A highly atropo-enantioselective – but *intramolecular* – synthesis of axially chiral

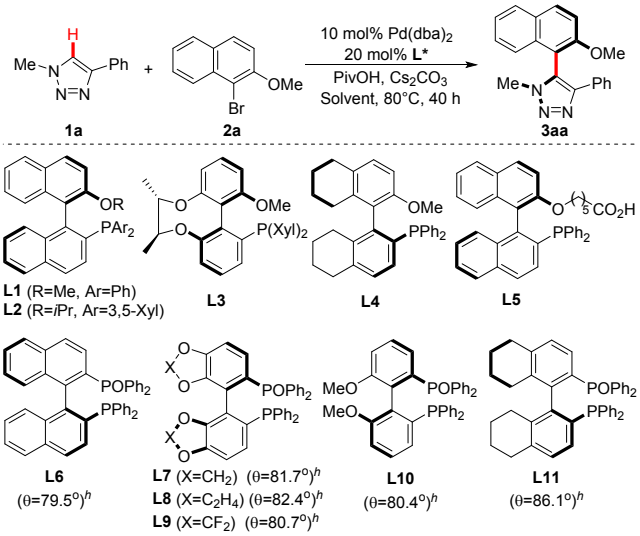
dibenzazepinones by a Pd(0)-catalyzed C–H arylation was reported by Cramer in 2018.[15] The void of efficient intermolecular atropo-enantioselective methods is in stark contrast to the rapid recent developments of asymmetric C–H functionalization technology.[16] Given the long-standing interest in asymmetric C–H functionalizations of our laboratories,[17] this challenged us to develop an intermolecular Pd(0)-catalyzed C–H arylation of electron-deficient heteroarenes constructing the heterobiaryl axis atropo-enantioselectively.

Despite being a common motif in biologically active compounds and usage as bioisostere and pharmacophore,[18] the atropisomeric behavior of 1,2,3-triazoles is rarely investigated.[19] Therefore, we selected 1-methyl-4-phenyl-1*H*-1,2,3-triazole (**1a**) and 1-bromo-2-methoxynaphthalene (**2a**) as suitable model substrates. 1,2,3-Triazoles are readily accessible by Cu-catalyzed azide-alkyne cycloadditions[20] and non-stereoselective Pd(0)-catalyzed C–H arylations have been reported.[21] The racemization barrier ($\Delta G^{\ddagger}_{enant}$)[22] of **3aa** was measured to be 32.4 kcal/mol in MeCN (see SI for details). This provides sufficient stability for the coupling products bearing four *ortho*-substituents around the heterobiaryl axis to withstand prolonged periods of heating at 80–100°C without significant racemization (Eq 1).



A brief initial screening revealed that $Pd(dba)_2$ with MOP (**L1**)[23] as ligand and pivalic acid as co-catalyst provided a very reactive catalytic system giving **3aa** in an excellent 95% yield and a proof of principle enantioselectivity of 67.5:32.5 (Table 1, Entry 1). Efforts to increase the sterics of **L1** replacing phenyl with 3,5-xylyl groups as well as exchanging methoxy for isopropoxy (**L2**) had virtually no effect on the enantioselectivity of **3aa** (entry 2). Variations of the dihedral angle of the ligand backbone, represented by **L3**[13c] and **L4**, marginally improved the selectivity for **L3** (Entry 3) but largely reduced it for **L4** (Entry 4). A bifunctional phosphine ligand with an attached carboxylic acid group (**L5**) developed by Baudoin[24] slightly improved the enantioselectivity to 73:27 (Entry 3). BINAPO (**L6**) improved the enantioselectivity for **3aa** to 78.5:21.5 albeit with a reduced yield of 36% (Entry 6). A switch to acetonitrile as solvent further improved the *er* to 85.5:14.5 with a significantly increased yield of 65% (Entry 7). Different bisphosphine monoxides (BPMOs)[25] such as SEGPHOSO (**L7**), SYNPHOSO (**L8**), DIFLUORPHOSO (**L9**), MeOBIPHEPO (**L10**) and H_8-BINAPO (**L11**) were prepared through a modified Grushin protocol in a single step.[26] Notably, the BPMO ligand type preferentially provided the opposite enantiomer compared to the MOP ligands. The enantioselectivity of **3aa** progressively improved from **L7** to **L11** (Entries 7–12). H_8-BINAPO (**L11**) performed best in terms of selectivity (95:5 *er*) and reactivity (79% yield) (Entry 12). This finding correlates with the very recently reported results from Larrosa on Pd(0)-catalyzed arylations of (η^6-arene)chromium complexes.[27] The observed enantioselectivity roughly correlates to the dihedral angle θ of the ligand, with a larger θ providing a higher enantioselectivity (Figure S1). Subsequent optimizations confirmed acetonitrile as the best solvent and Cs_2CO_3 outperformed other carbonates (entries 13–18). Notably, a broad screen of carboxylic acid additives revealed that they have a negligible impact on the enantioselectivity of this transformation (see SI). An increased concentration (0.67 M) improved the isolated yield of **3aa** to 93% keeping the er at 95:5 (Entry 19). The absolute configuration of product **3aa** was determined by X-ray crystallography to be *P* (Scheme 1).[28]

Table 1. Optimization of the Intermolecular Atroposelective C–H Arylation[a]

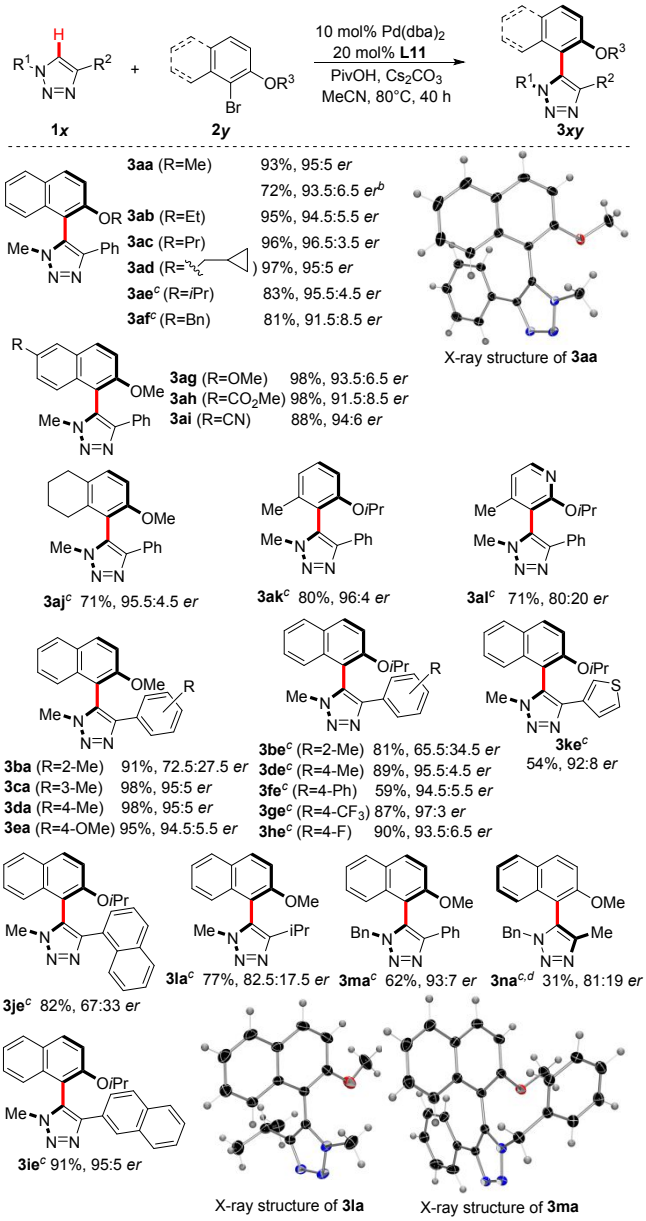


entry	L*	solvent	conc. [M]	% yield[b]	% *er*[c]
1	**L1**	dioxane	0.33	95	67.5:32.5
2	**L2**	dioxane	0.33	76	67.5:32.5
3	**L3**	dioxane	0.33	98	71.5:28.5
4	**L4**	dioxane	0.33	91	53.5:46.5
5[d]	**L5**	dioxane	0.33	88	73:27
6	**L6**	dioxane	0.33	36	78.5:21.5
7	**L6**	MeCN	0.33	65	85.5:14.5
8	**L7**	MeCN	0.33	57	12.5:87.5
9	**L8**	MeCN	0.33	34	12:88
10	**L9**	MeCN	0.33	26	10.5:89.5
11	**L10**	MeCN	0.33	62	10:90
12	**L11**	MeCN	0.33	79	95:5
13	**L11**	EtCN	0.33	59	94.5:5.5
14	**L11**	DME	0.33	53	92.5:7.5
15	**L11**	*t*BuOMe	0.33	48	92:8
16	**L11**	2-MeTHF	0.33	40	89.5:10.5
17	**L11**	dioxane	0.33	33	90:10
18[e]	**L11**	MeCN	0.33	<5	-
19[f]	**L11**	MeCN	0.67	93[g]	95:5

[a]50 µmol **1**, 75 µmol **2**, 5 µmol $Pd(dba)_2$, 10 µmol **L***, 15 µmol PivOH, 75 µmol Cs_2CO_3. [b]Determined by ^{1}H-NMR with trichloroethene as internal standard. [c]Determined by HPLC with a chiral stationary phase. [d]Without PivOH. [e]With K_2CO_3. [f]Double scale. [g]Isolated yield. [h]Calculated biaryl dihedral angle *θ* of **L*** in DFT-optimized $PdCl_2$**L*** complexes (see SI for details).

With the aforementioned conditions, the scope of the transformation was investigated (Scheme 1). We first focused on different bromonaphthalenes. Variation of the alkoxy group OR^3 *ortho* to the stereogenic axis of the products had little effect on both the reactivity and the enantioselectivity of the reaction (**3aa**–**3ad**). Bulkier groups (O*i*Pr and OBn) required higher reaction temperature (90°C) and extended reaction times to retain high yields. The selectivity of **3ae** remained very high (95.5:4.5 *er*), whereas it dropped to 91.5:8.5 *er* for **3af** due to a slow racemization at 90°C. The introduction of a further substituent at C6 of the naphthalene (**3ag**–**3ai**) had little influence on the reactivity and the stereoselectivity of the process. Noteworthily, the naphthalene ring is not required for the enantioselectivity. Indeed, tetrahydrobromonaphthalene **2j** and bromocresol derivative **2k** delivered coupling products **3aj** and **3ak** in good yield and excellent enantioselectivity. Moreover, bromopyridine **2l** was well arylated giving **3al** in good yield albeit a reduced 80:20 *er*. We next investigated the scope for the 1,2,3-triazole coupling partner **2*y***. Modifications of the aryl substituent of the 1,2,3-triazole were well tolerated and delivered coupling products **3*x*a** and **3*x*e** in consistently good yield and high atropo-enantioselectivity. The exceptions were the *o*-tolyl (**1b**) and 1-naphthyl groups (**1j**) where the increased steric demand of the substituent lowered the enantioselectivity of products **3ba**, **3be** and **3je**. In contrast, triazoles bearing a 2-naphthyl (**1i**) or thienyl unit (**1k**) reacted smoothly, with usual excellent atroposelectivity (**3ie**, **3ke**). Replacing the aryl substituent of the triazole by an aliphatic group (*i*Pr) had no influence on the reactivity and resulted in the formation of **3la** in 77% yield albeit with a reduced *er* of 82.5:17.5. Product **3na**, bearing a methyl group at the C4 position of the triazole was formed with similar enantiomeric ratio. Increasing the size of the nitrogen substituent (Me to Bn) did not impact the enantiomeric ratio, forming **3ma** in 93:7 *er* with 62% yield. X-ray crystallographic analysis of **3la** and **3ma** confirmed the absolute configurations of these two cases to be *P*.[28] Moreover, conducting the reaction with **1a** and **2a** at 10-fold scale provided **3aa** in 72% yield and 93.5:6.5 *er*.

Scheme 1. Scope for Atroposelective Intermolecular 1,2,3-Triazole Arylation[a]

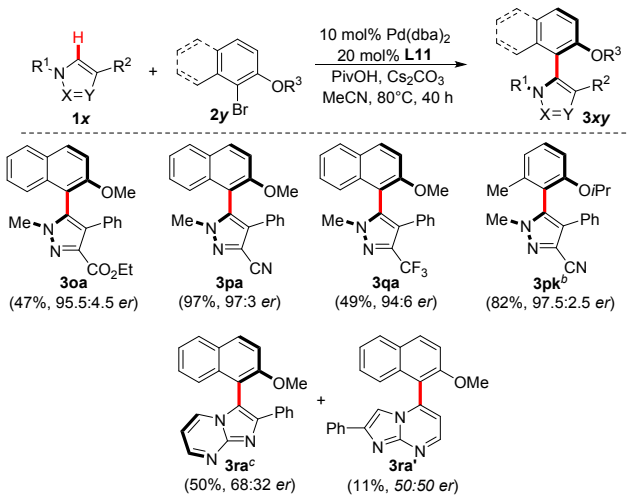


[a]0.1 mmol **1*x***, 0.15 mmol **2*y***, 10 mol% $Pd(dba)_2$, 20 mol% *(S)*-H_8-BINAPO, 30 mol% PivOH, 150 mol% Cs_2CO_3, MeCN (0.67 M), 80°C, 40 h; isolated yield. [b]On a 1.0 mmol scale of **1**. [c]90°C, 60 h. [d] *ent*-**L11** was employed. Absolute configurations assigned by analogy to **3la** and **3ma**.

The applicability of the transformation was challenged with related azoles (Scheme 2). We turned towards pyrazoles representing important building blocks for pharmaceuticals and agrochemicals.[29] Pleasingly, pyrazoles with electron-withdrawing groups at the 3-position underwent smooth and highly enantioselective C–H arylation. 3-Carbonitrile pyrazole **1p** was smoothly arylated with bromonaphthalene **2a** and bromocresol **2k**, forming **3pa** and **3pk** in excellent yields and enantioselectivities. The high atroposelectivity was maintained with an ester or a CF_3 group on the pyrazole instead of the nitrile substituent (**3oa**, **3qa**). Moreover, the arylation of 2-phenylimidazo[1,2-*a*]pyrimidine (**1r**), conducted at 100°C in dioxane, resulted in formation of the desired coupling product **3qa** in 50% yield and 68:32 *er*. Isomeric arylation product **3qa'** was detected in low levels and as racemic mixture. While the general feasibility of atroposelective C–H arylation of

heteroaromatics is herein proven with triazoles and pyrazoles, this example indicates that further tailored ligand and catalyst systems are required for other cases.

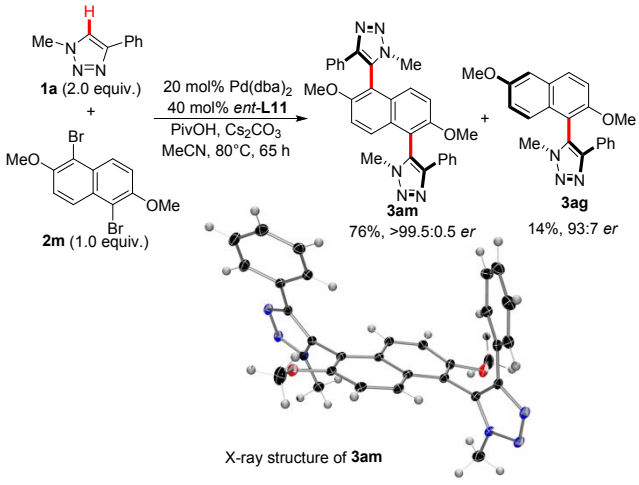
Scheme 2. Atroposelective Arylation of Pyrazoles and Imidazo[1,2-*a*]pyrimidine[a]



[a]0.1 mmol **1**, 0.15 mmol **2**, 10 µmol $Pd(dba)_2$, 20 µmol **L11**, 30 µmol PivOH, 0.15 mmol Cs_2CO_3, 0.67 M in MeCN at 80 °C for 40 h; isolated yield. [b]90°C for 60 h. [c]100°C for 40 h in dioxane. Absolute configurations assigned by analogy to **3la** and **3ma**.

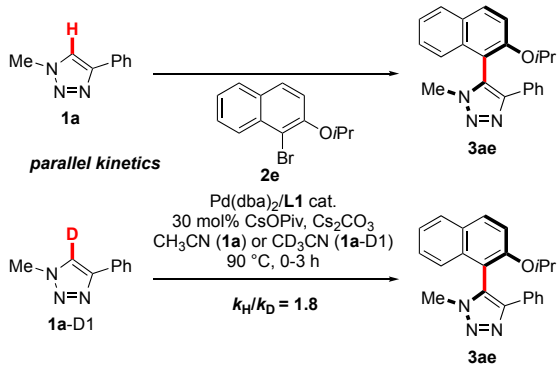
To probe the limits of the transformation, a double atroposelective[13f] C–H arylation of 1,5-dibromo-2,6-dimethoxynaphthalene **2m** and triazole **1a** was performed (Scheme 3). The reaction cleanly proceeded at 80°C, delivering the double C–H activation product **3am** possessing two stereogenic axes[30] in 76% yield (based on limiting **2m**) with an outstanding enantioselectivity of >99.5:0.5. Notably, no *meso*-isomer was observed, but compound **3ag** arising from one C–H arylation event and hydrodebromination of the second C–Br bond was formed in 14% yield and 93:7 *er*. X-ray analysis of **3am** allowed determination of the configuration of the axes to be *M,M*,[28] consistent with the fact that *ent*-**L11** was used for this reaction.

Scheme 3. Double Intermolecular Atroposelective C–H Arylation



To obtain further insights on the reaction mechanism and the critical steps of the catalytic cycle, the initial reaction rates (0–4 h reaction time) of protiated (**1a**) and deuterated (**1a**-D1) triazole substrates were compared (Scheme 4). Independent experiments performed with ligand **L1** provided a k_H/k_D value of 1.8. This value indicates that the C–H bond cleavage is the rate-limiting step of this reaction.[31] In addition, the structure of the carboxylic acid co-catalyst had an influence on the rate (the reaction was ca. 4 x faster with PivOH) but not on the enantioselectivity (Table S1). Taken together, these results indicate that the C–H activation step mainly operates through the concerted metallation-deprotonation mechanism and is rate-limiting.[32,33] Moreover, the effect of the ligand dihedral angle on the enantioselectivity tends to indicate that reductive elimination is the enantio-determining step of the reaction.

Scheme 4. Deuterium Kinetic Isotope Effect



In conclusion, we report a highly enantioselective intermolecular C–H arylation of medicinally relevant heteroarenes providing an efficient access to atropisomeric (hetero)biaryls. A Pd(0) complex equipped with H_8-BINAPO as chiral ligand enabled the arylation of a broad range of 1,2,3-triazoles in excellent yields and selectivities of up to 97:3 *er*. Besides triazoles, pyrazoles were arylated in high yields and excellent atropo-enantioselectivity. Moreover, the method was equally well suited for a stereoselective double arylation allowing the construction of two stereogenic axes with >99.5:0.5 *er*. The level of enantiocontrol seemed to be linked to the biaryl dihedral angle of the employed bisphosphine monoxide ligand. Mechanistic investigations indicated C–H activation as the rate-determining but not enantio-determining step. This provides a foundation to identify the origin of the selectivity in this process and to further extend the application potential of atroposelective C–H functionalization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website.

Experimental procedures and characterization data (PDF)

X-ray crystallographic cate for **3aa**, **3la**, **3ma** and **3am** (CIF)

Coordinates for DFT-optimized $PdCl_2$**L*** complexes (XYZ)

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Author Contributions

# Q.-H. N. & S.-M. G. contributed equally to this work.

Notes

The authors declare no competing financial interests.

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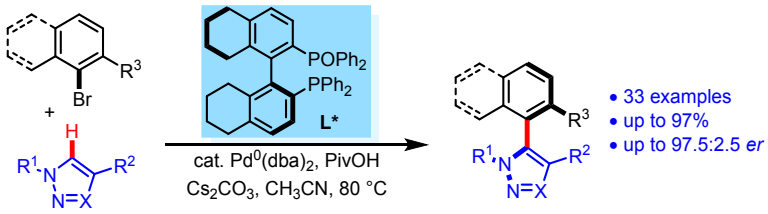
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• 33 examples
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