Article

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Pd-Catalyzed C–H Annulation of Five-Membered Heteroaryl Halides with Norbornene Derivatives

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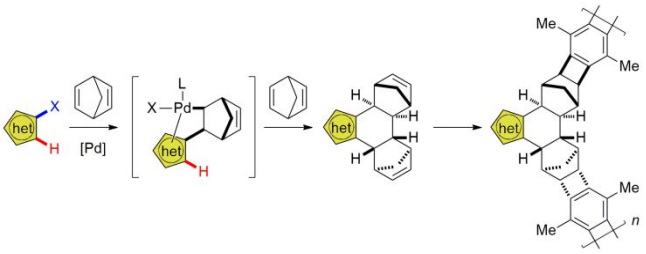
KEYWORDS. Catellani reaction, palladium catalysis, C−H bond functionalization, norbornadiene, ladder polymer

ABSTRACT: Complementary to Catellani-type reactions and 1:1 coupling of six-membered halo(hetero)arenes and norbornene (NBE) derivatives, Pd-catalyzed 1:2 coupling of five-membered haloheteroarenes with NBEs was achieved to afford rigid nonplanar heterocycles. Pyrazole, thiophene, furan, and indole underwent *exo*- and *trans*-selective annulation. Two strained alkene groups of the resulting products were further manipulated to afford 1-alkylindazoles and ladder polymers. The type of heteroarenes and position of halides along with the choice of ligands and bases were critical to set a preference between C–H annulation and Catellani reactions, which will be useful for the development of Pd-catalyzed, NBE-mediated reactions of heteroarenes.



Norbornene (NBE) derivatives represent an important class of unsaturated hydrocarbons in transition-metal-catalyzed reactions.[1] As rigid, strained bicyclic alkenes, NBEs readily undergo addition with organometallic species, yet the resulting NBE-metal adducts are not positioned for *syn*-β-hydride elimination. This unique characteristic of NBEs offers various reaction pathways, one of which is the Catellani reaction that has emerged as an effective strategy to provide functionalized aromatic compounds with high regiocontrol (Figure 1A, I).[2] Originally discovered and pioneered by Catellani and co-workers, the Pd/NBE cooperative catalysis enables simultaneous functionalization of both *ipso* and *ortho* positions of aryl halides in the presence of NBEs by Pd catalysts.[3] In this process, the formation of palladacycles with NBE is critical for the C–H functionalization of the *ortho* position, after which NBE is eventually released by β-carbon elimination.[4] Alternative to serving as the *ortho*-directing transient mediator, NBEs can be useful building blocks to construct rigid nonplanar molecular architectures (Figure 1A, II).[5,6] When NBE and related bridged (oxa)bicyclic alkenes are incorporated into polycyclic structures, it achieves structural curvature between fused rings, modulating intermolecular interaction in molecular recognition for the development of new drugs, ligands, and organic electronic materials.[7] Particularly in the annulation with norbornadiene (NBD), one of the strained alkene groups can be reserved for subsequent functionalization, such as addition- and annulation-polymerization.[1b-c,5e-f]

For the broad application of Pd-catalyzed, NBE-mediated reactions, many new approaches have been developed to overcome limitations in the scope of aryl halides.[8] One of the most notable constraints was the requirement of an *ortho*-substituent for selective mono-substitution, which was elegantly addressed by the development of new NBE derivatives.[9] The iodide constraint was also removed by careful selection of ligands and quenching nucleophiles, allowing for the use of aryl bromides for the Pd/NBE catalysis.[10]

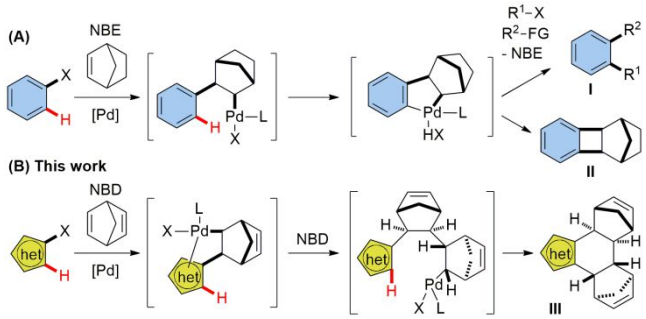


Figure 1. (A) Pd/NBE reactions of haloarenes generating difunctionalized arenes or cyclobutene rings. (B) Pd/NBD reactions of five-membered haloheteroarenes favoring *trans*- and 1:2-coupling selective annulation.

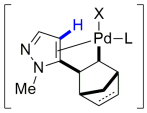
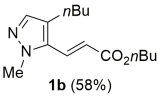
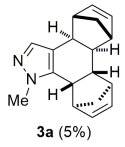
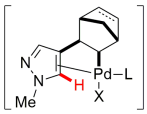
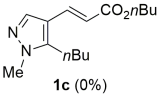
However, the Pd/NBE combination has been applied to heteroarene families with limited success. The type of heteroarenes and position of halides significantly impact oxidative addition and C–H activation steps, making it challenging to generalize the use of heteroaryl halides.[11] The Lautens group reported the Pd/NBE catalysis of haloheteroarenes for the first time, where 3-iodo(benzo)thiophenes and 1-tosyl-3-iodoindole afforded the

corresponding Catellani-type products, whereas 2-iodo counterparts were not suitable for this transformation.[12,13] Although the scope of heteroarenes has recently been expanded to include a few six-membered rings, key factors in controlling the reactivity of haloheteroarenes in the presence of NBEs have not been elucidated.[9,10a,14] More noticeably, only a couple of examples have been reported for the annulation of haloheteroarenes and NBEs despite that the reaction of readily available heteroarenes can offer straightforward methods to produce rigid, nonplanar polycyclic heteroarenes.[15]

We systematically studied Pd-catalyzed reactions of five-membered heteroaryl halides in the presence of NBEs (Figure 1B). It was envisioned that five-membered heterocycles would favor six-membered ring structures having two norbornyl bridges, such as III, if the formation of palladacycles were decelerated. By utilizing steric and coordinating effects of heteroarenes in combination with matching phosphine ligands and bases, *trans*- and 1:2-selective annulation of five-membered haloheteroarenes was achieved. The complementary reactivity patterns provide a guiding principle for the application of heteroaryl halides in the Pd-catalyzed, NBE-mediated reactions.

Based on Lautens group's observation, we envisioned that the position of a halide would be critical for promoting NBE-mediated processes of five-membered heterocyclic rings.[12] Pyrazole was selected as a model substrate because of easy preparation of both 4-and 5-halopyrazoles and steric effects adjustable by nitrogen substituents (Table 1).[16] Although 5-iodopyrazole **1a** underwent a Catellani-type reaction via the corresponding five-membered palladacycle by the Lautens protocol, such as I of Figure 1A,[12] only a small amount of the NBD adduct **3a** was obtained (entries 1 and 2). In contrast, the 4-iodo counterpart **2a** did not produce a detectable amount of the Catellani product such as **1c** (entry 3). However, **2a** was amenable for 1:2 annulation, giving **3a** in high yield.

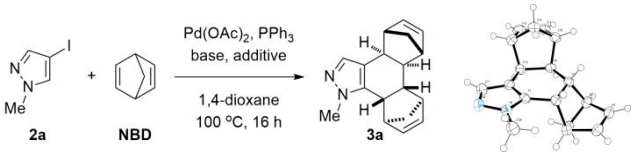
Table 1. Effect of the Iodide Position in Pd/NBE Reactions

entry	iodide	alkene	proposed intermediate	product
1[a]	 **1a**	NBE		 **1b** (58%)
2[b]		NBD		 **3a** (5%)
3[a]	 **2a**	NBE		 **1c** (0%)
4[b]		NBD		**3a** (79%)

[a]Reaction conditions: pyrazole (0.50 mmol), $Pd(OAc)_2$ (0.050 mmol), P(2-furyl)$_3$ (0.10 mmol), NBE (1.0 mmol), iodobutane (5.0 mmol), *n*-butyl acrylate (1.0 mmol), Cs_2CO_3 (2.5 mmol), MeCN (0.10 M), 80 ºC, 16 h (ref. 12). [b]Entry 5 of Table 2.

Control experiments found that the annulation product **3a** was readily prepared using a catalytic system derived from $Pd(OAc)_2$ and PPh_3, where the amount of NBD strongly influenced conversion (Table 2, entries 1 and 2). With optimal values being observed at 1:6 ratio between **2a** and NBD, higher relative amount of NBD resulted in the loss of efficiency, presumably due to a competition between NBD and PPh_3 for complexation with palladium (entry 3). The optimal ratio of Pd and PPh_3 was found to be 1:2, and in the absence of the phosphine, polymerization of NBD was observed (entries 4–7).[17] The addition of pivalic acid along with K_2CO_3 led to increased efficiency, presumably by facilitating C−H functionalization of the pyrazole ring, while replacing it with KOAc or KOPiv did not give comparable results (entries 8–10). The screening of solvents revealed that 1,4-dioxane was a better solvent for this reaction than toluene and DMA (entries 11 and 12). The structure of **3a** was analyzed by X-ray crystallography, showing the ladder-like structure with *trans*-geometry between the two bicyclic rings because of consecutive *exo*-selective addition to NBD.[18] The corresponding *cis*-isomer has not been observed because the steric hindrance should be large between the two norbornyl bridges fixed by the four-sp^3-carbon connectivity of the inner ring (see the Supporting Information for the DFT calculation and 2D NOESY spectra). It is also notable that compound **3a** was obtained as a racemic mixture (see the Supporting Information).

Table 2. Annulation of 4-Iodo-1-methylpyrazole with NBD[a]



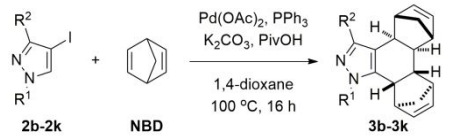
entry	NBD (eq.)	PPh_3 (mol%)	base	additive	**2a** (%)[b]	**3a** (%)[b]
1	4.0	20	K_2CO_3	PivOH	29	53
2	6.0	20	K_2CO_3	PivOH	17	71
3	8.0	20	K_2CO_3	PivOH	48	39
4	6.0	15	K_2CO_3	PivOH	0	83
5	6.0	10	K_2CO_3	PivOH	0	85 (79)
6	6.0	5.0	K_2CO_3	PivOH	0	83
7	6.0	0	K_2CO_3	PivOH	0	36
8	6.0	10	K_2CO_3	–	27	58
9	6.0	10	KOAc	–	47	32
10	6.0	10	KOPiv	–	0	69
11[c]	6.0	10	K_2CO_3	PivOH	19	67
12[d]	6.0	10	K_2CO_3	PivOH	15	38

[a]Reaction conditions: 4-iodo-1-methyl-1*H*-pyrazole (0.50 mmol), $Pd(OAc)_2$ (0.025 mmol), base (1.25 mmol), additive (0.15 mmol), 1,4-dioxane (0.25 M), 100 ºC, 16 h, under Ar. PivOH=pivalic acid. [b]^{1}H NMR yield. [c]Toluene was used instead of 1,4-dioxane. [d]DMA was used instead of 1,4-dioxane. Isolated yield in parentheses. ORTEP diagram of **3a** with anisotropic displacement parameters at 50% probability.

The 1:2 annulation reaction was found to be applicable to a variety of pyrazole derivatives (Table 3). Both *N*-alkyl- and aryl-substituted pyrazoles could be transformed to the corresponding polycyclic heterocycles in a single step (entries 1–7). It is notable that both a long-chain cetyl group and a sterically bulky isopropyl group at the pyrazole nitrogen were tolerated (entries 2 and 3). Furthermore, *N*-phenyl substituted pyrazole, which could potentially undergo the undesired pyrazole-directed C−H functionalization at the *N*-phenyl group,

showed efficient annulation of the pyrazole ring (entry 5).[19] Common nitrogen protecting groups, such as SEM and THP groups, could also be used in this process, indicating that functionalization of the pyrazole nitrogen at later stages would be feasible after deprotection (entries 8 and 9). In addition, a methyl group at the pyrazole C3 position was tolerated, and **3k** was obtained in a good yield (entry 10). In contrast, when the C5 position was blocked by a methyl group, such as 4-iodo-1,5-dimethyl-pyrazole, the annulation did not take place at the C3 and C4 positions (not shown).

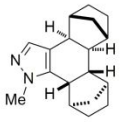
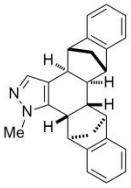
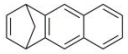
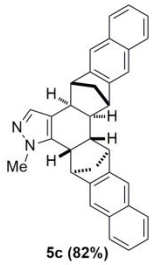
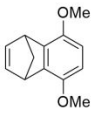
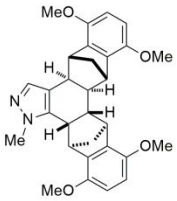
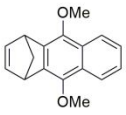
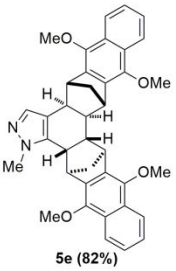
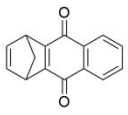
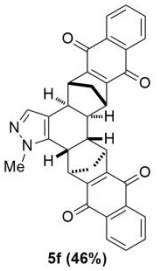
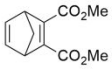
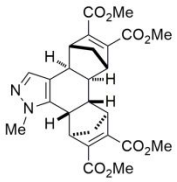
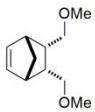
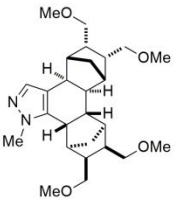
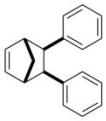
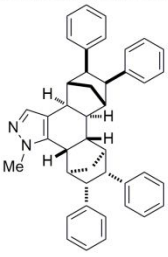
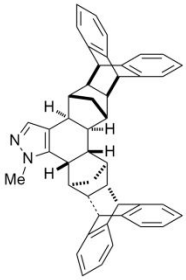
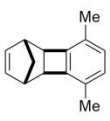
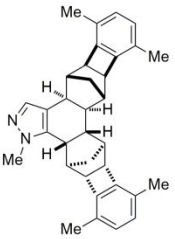
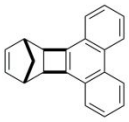
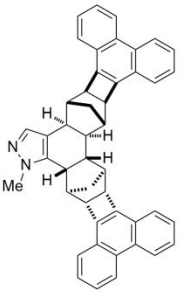
Table 3. Substrate Scope of Pyrazoles[a]



entry	R^1	R^2	yield (%)[b]
1	$CH_3CH_2CH_2CH_2$	H	**3b** (72)
2	$CH_3(CH_2)_{15}$ (Cetyl)	H	**3c** (76)
3	$(CH_3)_2CH$	H	**3d** (82)
4	nBuO$_2$CCH$_2$CH$_2$	H	**3e** (65)
5	C_6H_5	H	**3f** (66)
6	$C_6H_5CH_2$	H	**3g** (70)
7	$C_6H_5CH_2CH_2$	H	**3h** (69)
8	$(CH_3)_3SiCH_2CH_2OCH_2$ (SEM)	H	**3i** (75)
9	2-Tetrahydropyranyl (THP)	H	**3j** (57)[c]
10	CH_3	CH_3	**3k** (56)

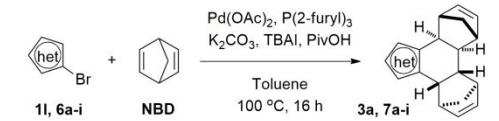
[a]Reaction conditions: 4-iodo-1-methyl-1*H*-pyrazole (0.50 mmol), norbornadiene (3.0 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.050 mmol), K_2CO_3 (1.25 mmol), PivOH (0.15 mmol), 1,4-dioxane (0.25 M), 100 °C, 16 h, under Ar. [b]Isolation yield. [c]The corresponding (NH)-free pyrazole was isolated after deprotection.

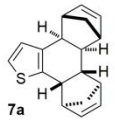
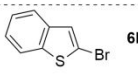
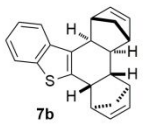
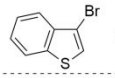
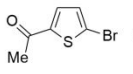
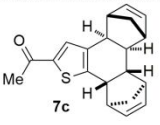
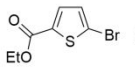
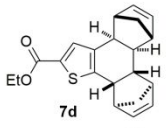
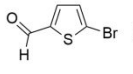
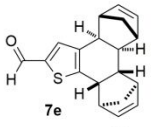
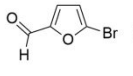
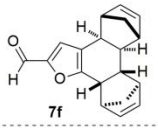
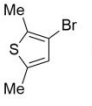
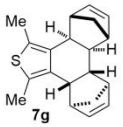
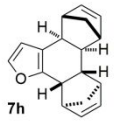
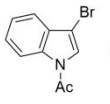
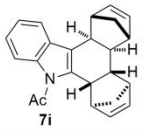
Table 4. Substrate Scope of Bridged Alkenes[a]

entry	reactant	product	entry	reactant	product	entry	reactant	product
1	 **4a**	 **5a (94%)**	2	 **4b**	 **5b (86%)**	3	 4c	 **5c (82%)**
4	 **4d**	 **5d (86%)**	5	 **4e**	 **5e (82%)**	6	 **4f**	 **5f (46%)**
7	 4g	 5g (92%)	8	 4h	 5h (67%)	9	 4i	 **5i (66%)**
10	 **4j**	 **5j (71%)**	11	 **4k**	 **5k (51%)**	12	 **4l**	 **5l (45%)**

[a]Reaction conditions: 4-iodo-1-methyl-1*H*-pyrazole (0.50 mmol), bridged alkene (3.0 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.050 mmol), K_2CO_3 (1.25 mmol), PivOH (0.15 mmol), 1,4-dioxane (0.25 M), 100 °C, 16 h, under Ar.

Table 5. Substrate Scope of Heteroarenes[a]



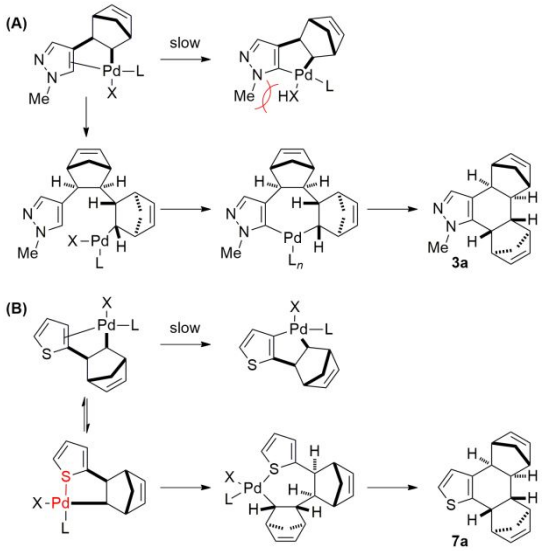
entry	reactant		product	yield
1		**6a**	 **7a**	70%
2		**6a'**		6% (20%)[c]
3		**6b**	 **7b**	61%
4		**6b'**		6% (11%)[c]
5		**6c**	 **7c**	75%
6		**6d**	 **7d**	63%
7		**6e**	 **7e**	61%
8		**6f**	 **7f**	55%
9		**2l**	**3a**	8% (63%)[b,c]
10		**6g**	 **7g**	0% (56%)[c]
11		**6h**	 **7h**	0% (27%)[c]
12		**6i**	 **7i**	41% (70%)[c]

[a]Reaction conditions: bromoheteroarene (2.5 mmol), norbornadiene (20 mmol), $Pd(OAc)_2$ (0.125 mmol), $P(2\text{-furyl})_3$ (0.50 mmol), K_2CO_3 (6.25 mmol), PivOH (0.75 mmol), TBAI (0.125 mmol), toluene (0.25 M), 100 °C, 16 h, under Ar. [b]The amount of norbornadiene was reduced (15 mmol). [c]Yields in parentheses were obtained using DPEPhos (0.188 mmol) instead of $P(2\text{-furyl})_3$.

Next, the scope of bridged bicyclic alkenes was investigated (Table 4). These bicyclic alkenes can be easily prepared by several conventional methods (see the Supporting Information). NBE and the benzenoid structures afforded the corresponding nonplanar nonconjugated heterocyclic compounds (entries 1–3). The methoxy and quinone groups as well as the ester functional groups were compatible to this protocol (entries 4–7). Norbornenes having both *endo*- and *exo*-substituents gave the corresponding annulation products (entries 8 and 9). Furthermore, multicyclic reactants readily underwent annulation reactions, allowing for a dramatic increase in molecular complexity in a single step (entries 10–12). This approach provided easy access to rigid polycyclic compounds, with two functional bicyclic bridges in a *trans* relationship. However, this method was not applicable to unstrained acrylate and styrene derivatives, which only gave the corresponding Heck products (Scheme S1).

To expand the scope of heteroarenes, five-membered heteroaryl bromides, more readily available but less reactive than iodide counterparts, were examined (Table 5 and see the Supporting Information). Ligands were replaced by either tri(2-furyl)phosphine or DPEPhos and a catalytic amount of TBAI was added. With $P(2\text{-furyl})_3$ as an optimal ligand, 2-bromo(benzo)thiophenes were superior to 3-bromo derivatives for the annulation (entries 1–4). This reactivity pattern is in contrast with the one of the Catellani reaction that was effective only with 3-bromo(benzo)thiophenes.[12] Thiophene and furan heterocycles having a bromide group adjacent to the heteroatom smoothly underwent annulation reactions (entries 5–8). In contrast, a Pd catalytic system using DPEPhos was more efficient than $P(2\text{-furyl})_3$ for heteroarenes having a bromide group distant from the heteroatom, presumably because they are less reactive for oxidative addition than the other regioisomeric bromides.[2] Using the DPEPhos conditions, 4-bromopyrazole **2l** was converted to the annulation product **3a** in 63% yield, slightly lower than the yield obtained with the iodide analogue **2a** (entry 9). Thiophene, furan, and indole heterocycles having a bromide at the C3 position successfully afforded the annulation products (entries 10–12).

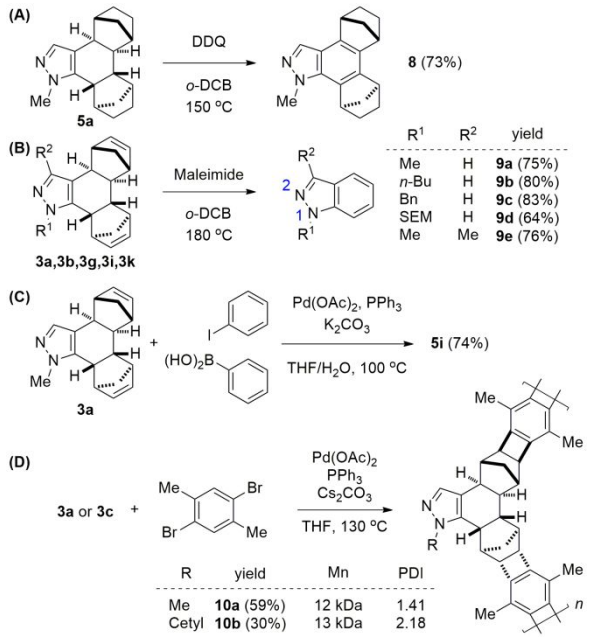
Scheme 1. Proposed Mechanisms



In addition to the ligand effect, these results consistently indicate that the C–H activation step is critical in Pd/NBE

processes (Scheme 1). The formation of the palladacycle can be retarded by the steric effect of the *N*-substituent (Scheme 1A, e.g. pyrazole **2a–k**, thiophene **6g**, and indole **6i**) and the coordinating effect of the heteroatom (Scheme 1B, e.g. thiophene **6a**–**6e** and furan **6f**).[21] It is also notable that in the latter set of the substrates, the available C–H bond is less reactive than the one at the heteroatom-connected carbon center for the formation of the palladacycle. In these cases, insertion to additional NBD took place, enabling the formation of the two-norbornyl-incorporated products.

Scheme 2. Application of the Resulting Annulation Products



The resulting polycyclic heterocycles could be further functionalized to yield a range of molecular structures in a divergent manner (Scheme 2). The oxidation of the newly formed six-membered ring rendered the central ring to be aromatic, giving a norbornyl protected indazole **8** (Scheme 2A). In addition, the presence of the bicyclic alkene moiety of the NBD adducts **3** allowed to perform *retro*-Diels-Alder reactions, where maleimide was used as a scavenging dienophile (Scheme 2B).[22] While typical *N*-alkylation of (NH)-free indazoles give a mixture of *N*1- and *N*2-alkylated regioisomers, our two-step procedure allowed for a selective synthesis of *N*1-alkylated indazoles **9a–e**.[2] As an alternative to the cyclization of 5,6-diphenyl NBE (Table 4, entry 9), a Pd-catalyzed diarylation reaction of the NBD adduct **3a** gave the tetraarylated polycycle **5i**, demonstrating that diarylation and cyclization can be carried out in any order (Scheme 2C).[2]

The versatility of the annulation products offers opportunities to produce new heterocycle-embedded polymers. Although polymerizations of functionalized norbornenes have been extensively studied, reports involving polymerization of heteroarene-containing norbornenes are scarce.[1b] When **3a** and **3c** were subjected to catalytic arene-norbornene annulation (CANAL) polymerization, developed by Xia and coworkers, the corresponding ladder polymers were obtained, showing annulated heterocycles can be useful monomers for the synthesis of heterocycle-containing ladder polymers (Scheme 2D).[5e-f] Incorporation of heterocycles into ladder polymers represents a powerful method of controlling the intermolecular interaction in this unique class of materials, a detailed study on which will be reported in due course.

In conclusion, we have developed a Pd-catalyzed 1:2 annulation reaction of five-membered heteroaryl halides with NBE derivatives. A variety of five-membered heteroaryl halides were investigated, which revealed the importance of the reactivity of the halide and C–H bond. When the formation of the five-membered palladacyle, a key intermediate of Catellani reactions, is slow due to steric and coordinating effects of heterocycles, 1:2 annulation is facilitated, giving diverse polycylic heterocycles containing synthetically useful strained alkenes. Conversely, if these factors can be eliminated, they can be useful substrates for Catellani-type reactions, which are currently under investigation.

ASSOCIATED CONTENT

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

Experimental procedures, compound characterization data, and NMR spectra (PDF)
Crystallographic data for **3a** (CIF)

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