Escape from Palladium: Nickel-Catalyzed Catellani Annulation

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ABSTRACT: While Catellani reactions have become increasingly important for arene functionalizations, they have been solely catalyzed by palladium. Here we report the first nickel-catalyzed Catellani-type annulation of aryl triflates and chlorides to form various benzocyclobutene-fused norbornanes in high efficiency. Mechanistic studies reveal a surprising outer-sphere concerted metalation deprotonation pathway during the formation of the nickelacycle, as well as the essential roles of the base and the triflate anion. The reaction shows a broad functional group tolerance and enhanced regioselectivity compared to the corresponding palladium catalysis.
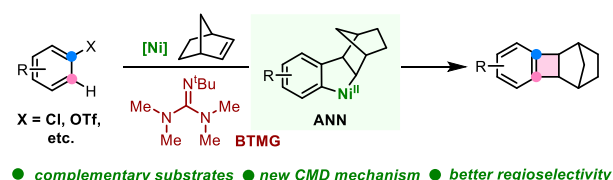
Palladium/norbornene (Pd/NBE) cooperative catalysis, also known as the Catellani-type reactions, has become an increasingly useful tool for arene functionalization (Scheme 1a).[1] The reaction typically starts with oxidative addition of Pd(0) with an aryl halide substrate, followed by migratory insertion into NBE and C−H palladation via concerted metalation deprotonation (CMD), to generate the key aryl-norbornyl palladacycle (ANP) intermediate. The ANP can subsequently react with an electrophile and a nucleophile (or an alkene) at ortho and ipso positions, respectively. This unusual vicinal difunctionalization proves to be valuable for streamlined syntheses of complex bioactive molecules, late-stage site-selective derivatizations, and access to unique polymers.[2] Alternatively, the ANP can undergo direct reductive elimination to provide an interesting benzocyclobutene-fused norbornane (BCN) product.[3]

Scheme 1. Catellani-type Annulation reactions

(a) Pd-catalyzed Catellani-type processes:

Catellani difunctionalization

reductive elimination

Catellani annulation
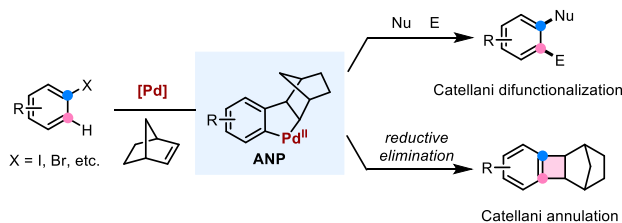
(b) This work: Ni-catalyzed Catellani annulation

● *complementary substrates* ● *new CMD mechanism* ● *better regioselectivity*

Such a Catellani annulation, also known as the catalytic arene-norbornene annulation reaction, has found elegant applications in synthesis of functional ladder-shaped organic materials.[4] While enormous advances have been made, the Catellani reactions have been exclusively catalyzed by Pd to date. Considering the high cost and net environmental impact associated with Pd usage,[5] there is a growing interest in exploring the potential
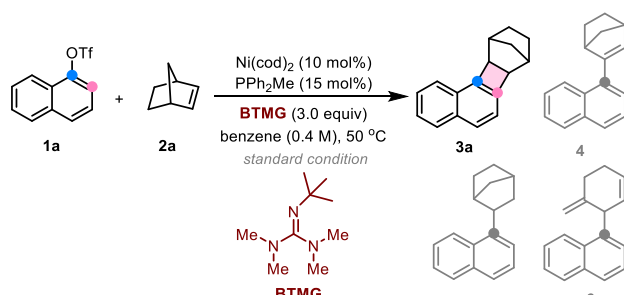
Scheme 2. Pd versus Ni in Catellani reactions
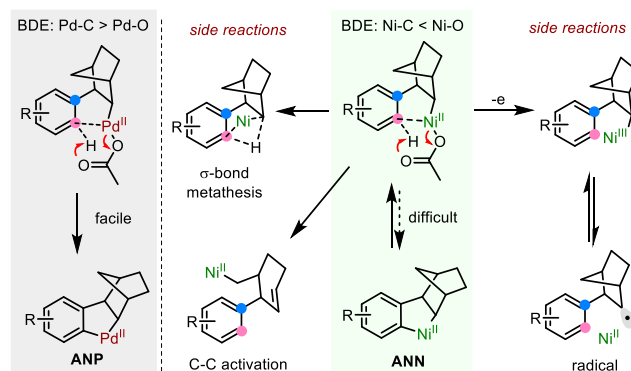
of earth-abundant metals as catalysts for Catellani-type reactions. In addition, the distinct properties of first-row metals may offer complementary reactivity and/or selectivity to the Pd catalysis, making them an attractive alternative.[6] As a progress towards the nickel (Ni)/NBE cooperative catalysis, here we describe our preliminary development of the first Ni-catalyzed Catellani annulation between aryl triflates/chlorides and NBEs (Scheme 1b).

While Ni catalysis proves to be powerful for many cross-coupling reactions,[7] substantial challenges could be imagined for realizing the Ni-catalyzed Catellani annulation. The key step is the formation of the aryl-norbornyl metallocycle, which requires a C−H metalation process (Scheme 2). For the Pd catalysis, the inner sphere CMD using an oxygen-derived X ligand (such as acetates or carbonates) as base is known to be facile.[8] In contrast to "soft" Pd, Ni is "harder" and much more oxophilic,[9] meaning that breaking a normal Ni−O bond would be energetically more difficult than breaking a Pd−O bond. In addition, given that Ni−C bonds are generally weaker than Ni−O bonds, formation of a nickelacycle could be thermodynamically unfavorable when common oxy-containing bases are used for CMD.[10] Also, after the migratory insertion the norbornyl group on the Ni(II) intermediate could compete as the base in the CMD process, leading to σ-bond metathesis side-products.[11] Furthermore, unlike Pd, Ni is more prone to trigger single-electron processes, which may lead to unusual side-products (e.g., formal β-hydrogen elimination product,

Table 1. Selected Optimization of the Ni-catalyzed Catellani annulation

Entry[a]	Variations from the standard condition	Yield of **3a/4/5/6** (%)[b]
1	**None**	**99/0/0/1**
2	w/o Ni(cod)$_2$	**0/0/0/0**
3	w/o PPh$_2$Me	**2/0/7/3**
4	w/o BTMG	**0/0/0/0**
5	other ligands instead of PPh$_2$Me	listed below
6	other base instead of BTMG	listed below
7	other solvent instead of benzene	listed below
8	1-bromonaphthalene instead of **1a**	**3/31/6/6**
9	1-iodonaphthalene instead of **1a**	**9/39/11/13**
10[c]	5 mol% Ni(cod)$_2$/7.5 mol% PPh$_2$Me was used	**82/0/9/4**

Ligand Effect	Base Effect	Solvent Effect
L2 : PPh$_3$, **40% yield**	**B2** : Cs$_2$CO$_3$, **4% yield**	**S2** : toluene, **93% yield**
L3 : PMe$_3$, **9% yield**	**B3** : PhOK, **2% yield**	**S3** : 1.4-dioxane, **91% yield**
L4 : xphos, **1% yield**	**B4** : DBU, **2% yield**	**S4** : MeCN, **71% yield**
L5 : dppe, **2% yield**	**B5** : Et$_3$N, **0% yield**	**S5** : DMA, **74% yield**
	B6 : ^{i}Pr$_2$NEt, **0% yield**	
	B7 : 2,6-Di-tert-butyl pyridine, **0% yield**	

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (0.4 mmol, 4.0 equiv), Ni(cod)$_2$ (0.01 mmol, 10 mol%), PPh$_2$Me (0.015 mmol, 15 mol%), BTMG (0.3 mmol, 3.0 equiv), benzene (0.25 mL), 50 °C, 48 h. [b]Yields were determined by ^{1}H NMR using CH$_3$NO$_2$ as an internal standard. [c]Reaction temperature was 70 °C.

vide infra).[12] Finally, Ni is known to be highly effective for activating strained C−C bonds;[13] therefore, cleavage of the strained NBE scaffold during the Ni catalysis is a concern that cannot be ignored.

To address the aforementioned challenges, we hypothesized that the choice of the base would be extremely critical to this reaction. After extensive exploration of various reaction conditions, the combination of an aryl triflate and a bulky organic base, i.e., 2-*tert*-butyl-1,1,3,3-tetramethyl-guanidine (BTMG) gave the most promising results (Table 1). When 1-naphthyl triflate **1a** was employed as the model substrate, to our delight, the desired annulation BCN product **3a** was obtained in 99% yield using Ni(cod)$_2$ as catalyst, PPh$_2$Me as ligand, BTMG as base in benzene at 50 °C (Table 1, entry 1). Control experiments showed that Ni(cod)$_2$, PPh$_2$Me and BTMG were all essential to this transformation (entries 2-4). PPh$_2$Me appears to be a superior ligand; when using PPh$_3$ instead, only 40% yield of **3a** were obtained (entry 5). Other phosphine ligands, such as PMe$_3$, xphos and dppe, were not effective. BTMG has been the best base for this reaction. Oxygen-containing bases, e.g., Cs$_2$CO$_3$ and PhOK, were found to inhibit this reaction (entry 6). Other organic bases gave nearly no desired product under the current conditions (entry 6). Note that the reaction

can run smoothly in a range of solvents with vastly different polarity (entry 7). In contrast to aryl triflates, the corresponding bromide or iodide substrates gave a significant amount of side products (**4-6**) (entries 8 and 9). The unusual *β*-hydrogen elimination product (**4**) is likely generated via homolytic cleavage of Ni−C bonds promoted by single-electron transfer processes.[14] Side-product **5** is proposed to form via *σ*-bond metathesis supported by the deuterium labelling[15] and/or through hydride transfer, while the NBE-ring-opening product (**6**) was likely yielded from a *β*-carbon elimination process. These results suggest that halide anions could poison the catalyst, leading to undesired pathways. Finally, satisfactory yield could still be obtained when decreasing the catalyst loading to 5 mol% and running the reaction at a slightly higher temperature (entry 10).

Scheme 3. Experimental Mechanistic Study

(a) Kinetic isotopic effects

Intermolecular competition : $k_H/k_D = 2.0$
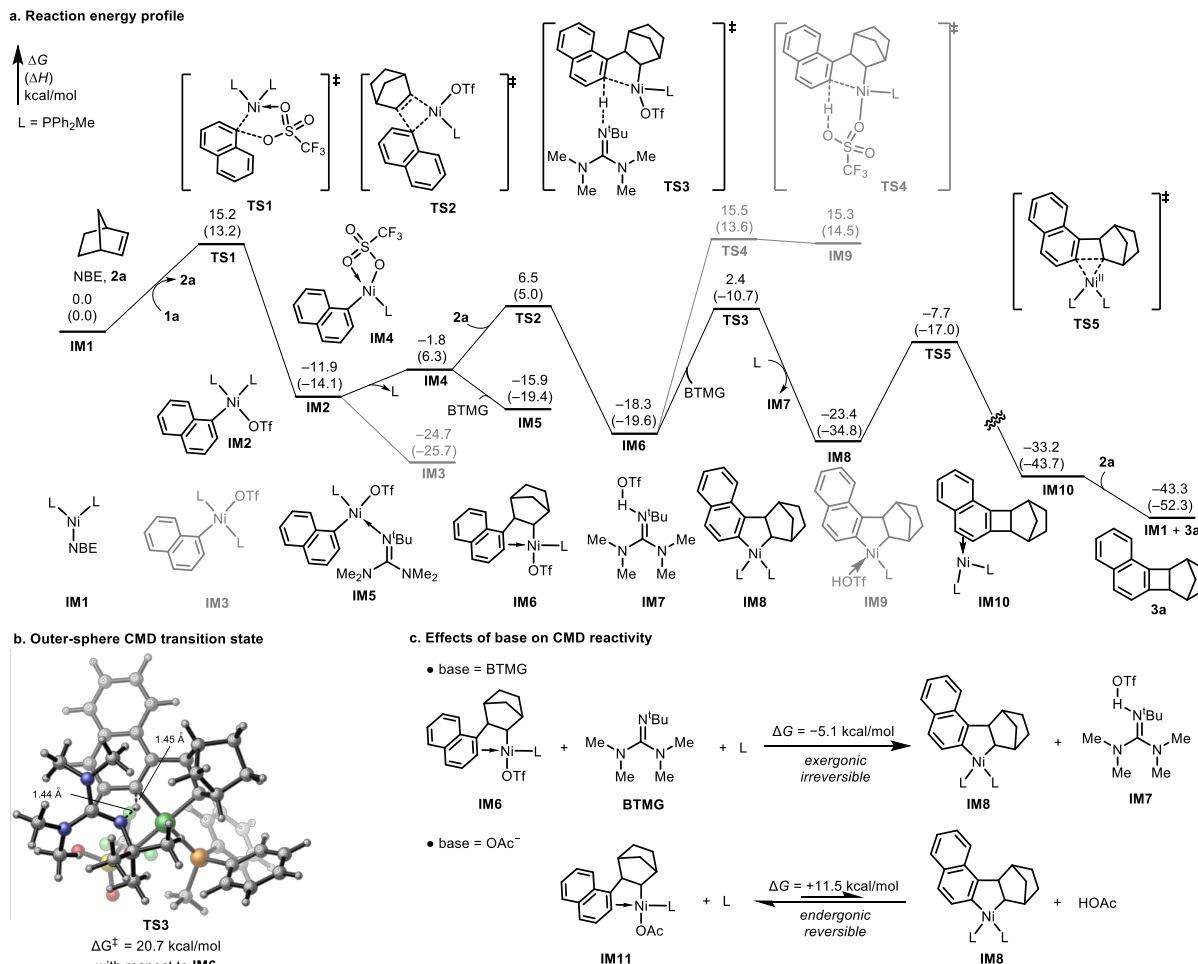Parallel experiment : $k_H/k_D = 1.1$-1.4
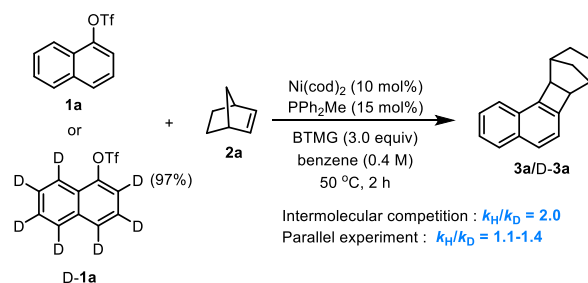
(b) Determination of the kinetic order
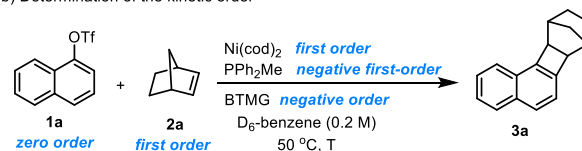
Intrigued by the unique catalytic system, the reaction mechanism was investigated through a combined effort between experiments and calculations. First, the kinetic isotope effect (KIE) of the reaction was measured between **1a** and fully deuterated **D-1a** (Scheme 3a). The parallel experiment gave a KIE value of 1.1-1.4, and the competition KIE showed a slightly higher value of 2. The lack of significant primary KIE in these experiments suggests that C−H cleavage may not be directly involved in the turnover-limiting step (TLS). Next, the kinetic study revealed that the reaction exhibits a first-order dependence on concentrations of Ni(cod)$_2$/PPh$_2$Me and NBE, but a zero-order on the concentration of 1-naphthyl triflate (Scheme 3b). These data indicate that oxidative addition of the aryl triflate with Ni(0) is a fast process and should not be the TLS. In addition, the negative orders on PPh$_2$Me and BTMG were observed, which implies that the resting state(s) of the catalyst should contain BTMG and PPh$_2$Me, and their dissociations are needed either before or during the TLS.[16]

Next, we performed density functional theory (DFT) calculations to explore the mechanism of the Ni-catalyzed annulation and the origins of the effects of base and aryl triflate on reactivity.[17] The computed reaction energy profile (Figure. 1a) revealed that the reaction undergoes five-membered cyclic oxidative addition of ArOTf (**1a**) to bisphosphine-ligated Ni(0) species with a relatively low Gibbs free energy barrier of 15.2 kcal/mol (**TS1**, less favorable oxidative addition transition state isomers are included in the Supporting Information).
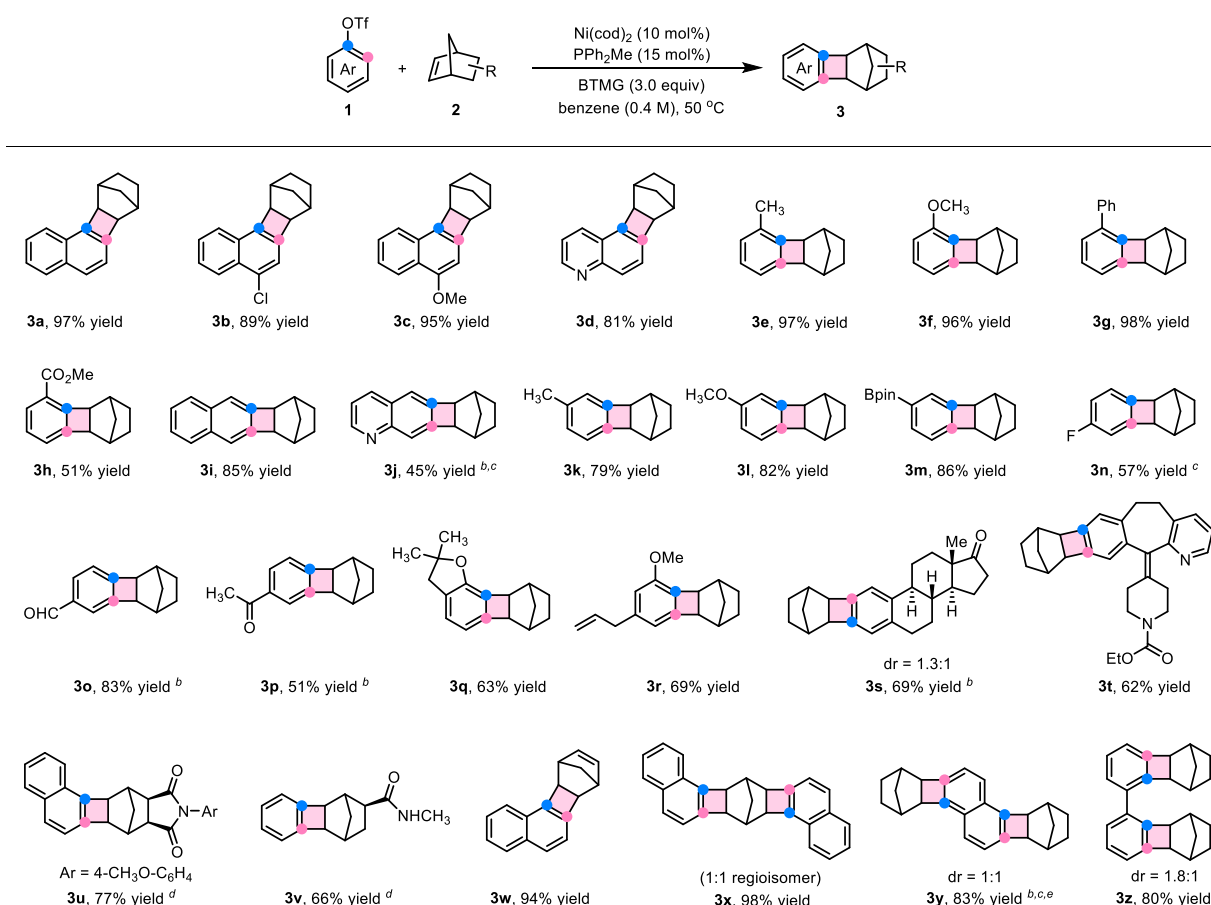
a. Reaction energy profile

b. Outer-sphere CMD transition state

TS3
ΔG‡ = 20.7 kcal/mol
with respect to **IM6**

c. Effects of base on CMD reactivity

- base = BTMG

IM6 + BTMG + L → ΔG = −5.1 kcal/mol *exergonic irreversible* → IM8 + IM7

- base = OAc⁻

IM11 + L ⇌ ΔG = +11.5 kcal/mol *endergonic reversible* ⇌ IM8 + HOAc

Figure. 1. Free energy profile of the Ni-catalyzed annulation of aryl triflates. All energies were calculated at M06/SDD−6-311+G(d,p), SMD(benzene)//B3LYP-D3/LANL2DZ−6-31G(d) level of theory.

After the oxidative addition that directly leads to the *cis* bisphosphine complex **IM2**, several off-cycle Ni(II) complexes are formed, including *trans* bisphosphine complex **IM3** (see Supporting Information for the X-ray crystal structure) formed *via* cis/trans isomerization, and a monophosphine-ligated complex **IM5** formed via dissociative ligand exchange (via **IM4**) to replace one of the PPh$_2$Me ligands with BTMG. Subsequent migratory insertion of NBE occurs via a monophosphine-ligated transition state (**TS2**) to form alkyl Ni(II) complex **IM6**. From **IM6,** the most favorable C–H metalation pathway involves an unusual outer-sphere CMD[18] via **TS3**, in which the base, BTMG, is not bound to the Ni center (Figure 1b). The alternative inner-sphere CMD pathway involving a six-membered cyclic TS with triflate as the base (**TS4**) is much less favorable because of the low basicity of triflate. Although the triflate anion is not serving as the base, it plays an important role in the CMD step. The triflate-bound Ni(II) center is sufficiently electron-deficient to promote the ortho C–H deprotonation.[19] The computed NPA charges indicate that the Ni(II) becomes less positively charged in the CMD transition state (e(Ni) = 0.290 in **TS3** compared to 0.336 in **IM6**, consistent with an electrophilic C–H activation process.[20] In addition, formation of a stable guanidinium triflate salt makes the C–H metalation step exergonic ($\Delta G_{IM6\rightarrow IM8}$ = −5.1 kcal/mol. See Figures 1c and Figure S10 for a compari-

son of CMD reactivity and reaction energies of triflate-bound **IM6** and other Ni(II) complexes). After the outer-sphere CMD, ANN **IM8** is formed. Subsequent C–C bond reductive elimination via **TS5** (15.7 kcal/mol with respect to **IM8**) delivers the desired BCN product **3a**. Based on the computed reaction energy profile, the TLS in the catalytic cycle is migratory insertion (**TS2**). This is consistent with the kinetics studies (Scheme 3b) that indicate first-order dependence on [**2a**] and [Ni(cod)$_2$], and negative orders for PPh$_2$Me and BTMG, because both can serve as catalyst inhibitors prior to the rate-determining NBE migratory insertion step.

Next, the origin of the enhanced reactivity using BTMG as base was investigated. Experimentally, the use of BTMG leads to substantially higher yield than oxygen-containing bases, such as Cs$_2$CO$_3$ and CsOAc, which are commonly used in the Pd/NBE catalysis and other Pd-catalyzed C−H functionalization reactions. Our DFT calculations indicated that the outer-sphere CMD of **IM6** with BTMG is exergonic by 5.1 kcal/mol, whereas the C−H metalation of an analogous alkyl Ni(II) acetate complex **IM11** is endergonic by 11.5 kcal/mol (Figure 1c). These calculations indicate that BTMG provides much stronger thermodynamic driving force to promote the C−H metalation than oxygen-containing bases, which bind much more strongly to the pre-CMD Ni(II) complex. The steric

Table 2. Nickel-catalyzed annulation of aryl triflates with NBEs [a]

Reaction scheme: 1 + 2 → 3, conditions: Ni(cod)₂ (10 mol%), PPh₂Me (15 mol%), BTMG (3.0 equiv), benzene (0.4 M), 50 °C

3a, 97% yield
3b, 89% yield
3c, 95% yield
3d, 81% yield
3e, 97% yield
3f, 96% yield
3g, 98% yield

3h, 51% yield
3i, 85% yield
3j, 45% yield [b,c]
3k, 79% yield
3l, 82% yield
3m, 86% yield
3n, 57% yield [c]

3o, 83% yield [b]
3p, 51% yield [b]
3q, 63% yield
3r, 69% yield
dr = 1.3:1
3s, 69% yield [b]
3t, 62% yield

Ar = 4-CH₃O-C₆H₄
3u, 77% yield [d]
3v, 66% yield [d]
3w, 94% yield
(1:1 regioisomer)
3x, 98% yield
dr = 1:1
3y, 83% yield [b,c,e]
dr = 1.8:1
3z, 80% yield

[a]Reaction conditions: **1** (0.3 mmol, 1.0 equiv), **2** (1.2 mmol, 4.0 equiv), Ni(cod)₂ (0.03 mmol, 10 mol%), PPh₂Me (0.045 mmol, 15 mol%), BTMG (0.9 mmol, 3.0 equiv), benzene (0.75 mL), 50 °C, 48 h. Isolated yields are reported. [b]70 °C. [c]72 h. [d]90 °C. [e]**2** (8.0 equiv), Ni(cod)₂ (20 mol%), PPh₂Me (30 mol%), BTMG (6.0 equiv), benzene (1.5 mL).

hinderance of BTMG prevents it from binding to the sterically encumbered Ni center in **IM6**. On the other hand, when a strongly-coordinating acetate anion is present, a stable Ni(II) acetate complex (**IM11**) is formed, leading to thermodynamically less favorable C−H metalation. Altogether, the computational studies highlighted several important factors on reactivity, such as the unique roles of triflate anion and BTMG in the outer-sphere CMD step—*distinct mechanistic features that are not previously observed in analogous palladium-catalyzed reactions.*
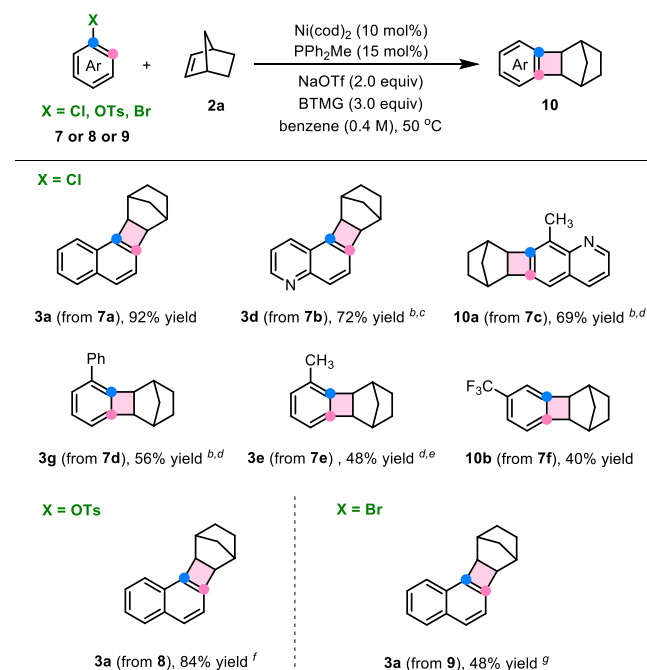
The scope of this annulation reaction was next examined under the standard conditions. As shown in Table 2, various aryl triflates could produce the corresponding BCN products in good to excellent yield under mild conditions. Functionalized naphthyl triflates, including Cl (**3b**) or OMe (**3c**)-substituted ones, all worked efficiently. 5-Quinolinyl triflate (**3d**) was also a suitable substrate for this transformation. Besides, ortho-substituted phenyl triflates (**3e-h**), such as those containing an ortho methyl (**3e**), methoxyl (**3f**), phenyl (**3g**) or ester group (**3h**), could all be tolerated and give the expected products in excellent yield. Gratifyingly, the reactions of meta-substituted aryl triflates proceeded smoothly to produce the cyclobutanated products with nearly complete site-selectivity.[21] 2-Naphthyl triflate (**3i**) delivered the desired product with annulation at the less sterically hindered C3 position, albeit that 5-quinolinyl (**3j**) triflate was less reactive.

Other functional groups, including boronate (**3m**), fluoride (**3n**), formyl (**3o**) and acetyl (**3p**) groups, were all compatible. In addition, para-substituted aryl triflates also worked well. Furthermore, substrates derived from various natural products, such as carbofuran phenol (**3q**), eugenol (**3r**), estrone (**3s**) and loratadine (**3t**), uneventfully delivered the desired annulation products. Apart from simple NBE, functionalized NBEs (**3u-w**) were also competent coupling partners. Note that, **3w** synthesized from norbornadiene could further react with 1-naphthyl triflate **1a** to give the doubly annulated product **3x** in excellent yield as a 1:1 regioisomer. Reactions with ditriflates (**3y** and **3z**) also occurred in good yield.

To the best of our knowledge, regular aryl chlorides have not been used as substrates in Catellani reactions.[1] However, Ni complexes are known to be generally efficient for oxidative addition with aryl chlorides.[7] To show the merit of this Ni-catalyzed Catellani reaction, aryl chlorides were next explored as the substrates (Table 3). Our mechanistic study shows that an electron-deficient Ni center would facilitate the base-mediated outer-sphere CMD (vide supra), which is the reason that normal aryl halides are not effective substrates under the standard conditions. Here we hypothesize that, by adding an additive that can replace the halide ligand with triflate, the same reactive pre-CMD intermediate could be generated. Indeed, when NaOTf was used as additive, various aryl chlorides now worked well to afford the desired products (**3a**, **3d**,

Table 3. Nickel-catalyzed annulation of aryl chlorides and tosylates

Ni(cod)$_2$ (10 mol%)
PPh$_2$Me (15 mol%)
NaOTf (2.0 equiv)
BTMG (3.0 equiv)
benzene (0.4 M), 50 °C

X = Cl, OTs, Br
7 or 8 or 9   +   2a   →   10

X = Cl

3a (from **7a**), 92% yield

3d (from **7b**), 72% yield [b,c]

10a (from **7c**), 69% yield [b,d]

3g (from **7d**), 56% yield [b,d]

3e (from **7e**), 48% yield [d,e]

10b (from **7f**), 40% yield

X = OTs

3a (from **8**), 84% yield [f]

X = Br

3a (from **9**), 48% yield [g]

[a]Reaction conditions: **7/8/9** (0.1 mmol, 1.0 equiv), **2** (4.0 equiv), Ni(cod)$_2$ (10 mol%), PPh$_2$Me (15 mol%), NaOTf (2.0 equiv), BTMG (3.0 equiv), benzene (0.25 mL), 50 °C, 48 h. Isolated yields are reported. [b]Ni(cod)$_2$ (15 mol%), PPh$_2$Me (22.5 mol%), NaOTf (1.0 equiv). [c]80 °C. [d]90 °C. [e]Ni(cod)$_2$ (15 mol%), PPh$_2$Me (22.5 mol%), NaOTf (2.0 equiv). [f]Ni(cod)$_2$ (10 mol%), PPh$_2$Me (15 mol%), 70 °C. [g]Ni(cod)$_2$ (10 mol%), PPh$_2$Me (15 mol%), NaOTf (1.0 equiv).

10a, **3g**, **3e**, **10b**) in good yields. Under a similar condition, 1-bromonaphthalene worked with moderate efficiency. Besides triflates, aryl tosylates (**9**) also appear to exhibit excellent reactivity.

Control of the site-selectivity for meta-substituted substrates in Catellani reactions has not been a trivial issue when Pd was used as the catalyst.[3,22] As illustrated in Table 4, the site-selectivity with Pd catalysis ranged from good to poor.[3b] In contrast, the Ni catalysis showed significantly improved site-selectivity (3-5 folds better) for these challenging substrates. It is likely that the outer-sphere CMD, mediated by a bulky BTMG base, is more sensitive to sterics than the normal inner-sphere CMD, leading to enhanced site-selectivity.

In summary, we have developed the first Ni-catalyzed Catellani annulation of aryl triflates and chlorides, which opens the door for introducing earth-abundant-metal catalysis to this type of transformations. The high reaction efficiency, broad functional group tolerance, complementary substrate scope and enhanced site-selectivity could make Ni catalysis a promising alternative to Pd. The new outer-sphere CMD mechanism uncovered in this reaction could have broad implications for developing other Ni-catalyzed C−H functionalization reactions. Efforts on developing the Ni-catalyzed Catellani difunctionalization are ongoing.

Table 4. Site-selectivity comparison of Ni and Pd catalysis[a]

condition A : Ni(cod)$_2$ (10 mol%)
PPh$_2$Me (15 mol%)
BTMG (3.0 equiv)
benzene (0.4 M)
50 °C or 70 °C

condition B : Pd$_2$(dba)$_3$ (1 mol%)
CyJohnPhos (4 mol%)
K$_2$CO$_3$ (2.0 equiv)
dioxane (0.4 M), 120 °C

1k, 1l, 1j   +   2a   →   Ar

Regioselectivity = ● : ●

Entry[a]	Substrate	Regioselectivity under condition A	Regioselectivity under condition B
1	1k	40:1	17:1
2	1l	36:1	6.7:1
3	1j	4:1[b]	1.3:1

[a]Condition A: **1k/1l/1j** (0.1 mmol, 1.0 equiv), **2a** (4.0 equiv), Ni(cod)$_2$ (10 mol%), PPh$_2$Me (15 mol%), BTMG (3.0 equiv), benzene (0.25 mL), 50 °C, 48 h. Condition B: **1k/1l/1j** (0.1 mmol, 1.0 equiv), **2a** (1.5 equiv), Pd$_2$(dba)$_3$ (1.0 mol%), CyJohnphos (4 mol%), K$_2$CO$_3$ (2.0 equiv), 1,4-dioxane (0.25 mL), 120 °C. The yields and ratio of two isomers were determined by ^{1}H-NMR with CH$_3$NO$_2$ as internal standard. [c]70 °C was used.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."
Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2254808 contain the supplementary crystallographic data for this paper. This data can be obtained. free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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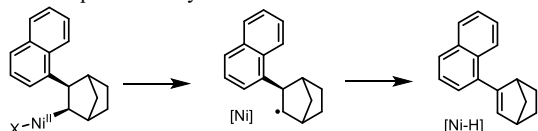
(15) see Supplementary Information 4.2 for details.

(16) For a preliminary exploration of the resting state(s) and detailed discussions, see Supporting Information 4.3.

(17) DFT calculations were performed at the M06/SDD–6-311+G(d,p), SMD(benzene)//B3LYP-D3/LANL2DZ–6-31G(d) level of theory. Translational entropies in benzene solvent were computed using the "free-volume" theory described by Whitesides: *J. Org. Chem.* **1998**, *63*, 3821-3830.

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Nickel-Catalyzed *Catellani Annulation*

X = Cl, OTf, etc.

[Ni]

BTMG

● *complementary substrates* ● *outer-sphere CMD* ● *better regioselectivity*