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Modular Entry to Functionalized Tetrahydrobenzo[*b*]azepines via the Palladium/Norbornene Cooperative Catalysis Enabled by a C7-Modified Norbornene

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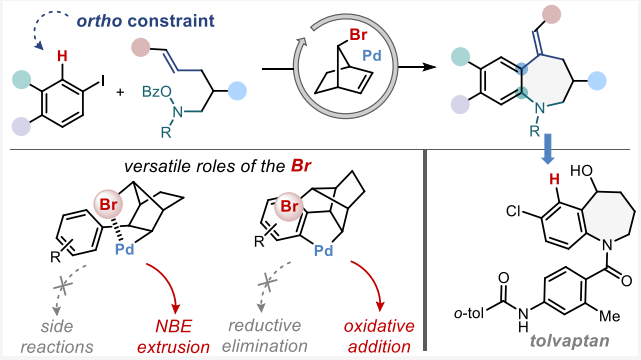
ABSTRACT: Tetrahydrobenzo[*b*]azepines (THBAs) are commonly found in many bioactive compounds; however, the modular preparation of functionalized THBAs remains challenging to date. Here, we report a straightforward method to synthesize THBAs directly from simple aryl iodides via palladium/norbornene (Pd/NBE) cooperative catalysis. Capitalizing on an olefin-tethered electrophilic amine reagent, an ortho amination followed by 7-*exo*-trig Heck cyclization furnishes the seven-membered heterocycle. To overcome the difficulty with ortho-unsubstituted aryl iodide substrates, we discovered a unique C7-bromo-substituted NBE (**N1**) to offer the desired reactivity and selectivity. In addition to THBAs, synthesis of other benzo-seven-membered ring compounds can also be promoted by **N1**. Combined experimental and computational studies show that the C7-bromo group in **N1** plays an important and versatile role in this catalysis, including promoting *β*-carbon elimination, suppressing benzocyclobutene formation, and stabilizing reaction intermediates. The mechanistic insights gained could guide future catalyst design. The synthetic utility has been demonstrated in a streamlined synthesis of tolvaptan and forming diverse pharmaceutically relevant THBA derivatives. Finally, a complementary and general catalytic condition to access C6-substituted THBAs from ortho-substituted aryl iodides has also been developed.



INTRODUCTION

Seven-membered nitrogen-containing heterocycles represent an important class of pharmacophores and exhibit a broad spectrum of biological activities.[1] In particular, the tetrahydrobenzo[*b*]azepine (THBA) ring system has been found in a number of marketed drugs, such as tolvaptan[2] and benazepril,[3] and other bioactive compounds[4] (Figure 1). However, compared to their six- or five-membered counterparts—tetrahydroquinolines and indolines—synthesis of functionalized THBAs still represents a substantial challenge because of limited approaches to accessing medium-sized heterocycles in an efficient and modular manner.

Conventional methods of preparing THBAs, including annulation,[5] ring expansion,[6] and aryne strategies,[7] usually take a multistep sequence and/or have limited scopes (Scheme 1, top). In addition, vicinal difunctionalized arenes are needed with these methods. For comparison, the use of intramolecular C−H functionalization to construct the C−C bond in THBAs, via either Friedel−Crafts[8] or transition-metal catalysis,[9,10] avoids complex arene precursors and simplifies the synthesis (Scheme 1, middle). Although they clearly represent more attractive strategies to access THBAs, the availability of the corresponding elaborated aniline substrates cannot be ignored.

Recently, the palladium/norbornene (Pd/NBE) cooperative catalysis, originally discovered by Catellani,[11] has emerged as a useful tool for modular arene synthesis.[12] Through forming a unique aryl-norbornyl-palladacycle (ANP) intermediate, simultaneous functionalizations of ortho and ipso positions of aryl halides can take place through selective coupling with an electrophile and a nucleophile, respectively. In particular, Lautens has pioneered the demonstration of fused-ring construction using electrophile/nucleophile-tethered reagents.[13] Complementary to the C−C bond-forming C−H functionalization approaches, the Pd/NBE-catalyzed tandem ortho C−H amination[14] followed by an intramolecular ipso Heck cyclization[15] can provide a straightforward and modular strategy to access diverse THBAs (Scheme 1, bottom).

Although this direct annulation approach to constructing THBAs may seem to be straightforward, a number of key issues remain to be addressed (Scheme 2). First, almost all the Pd/

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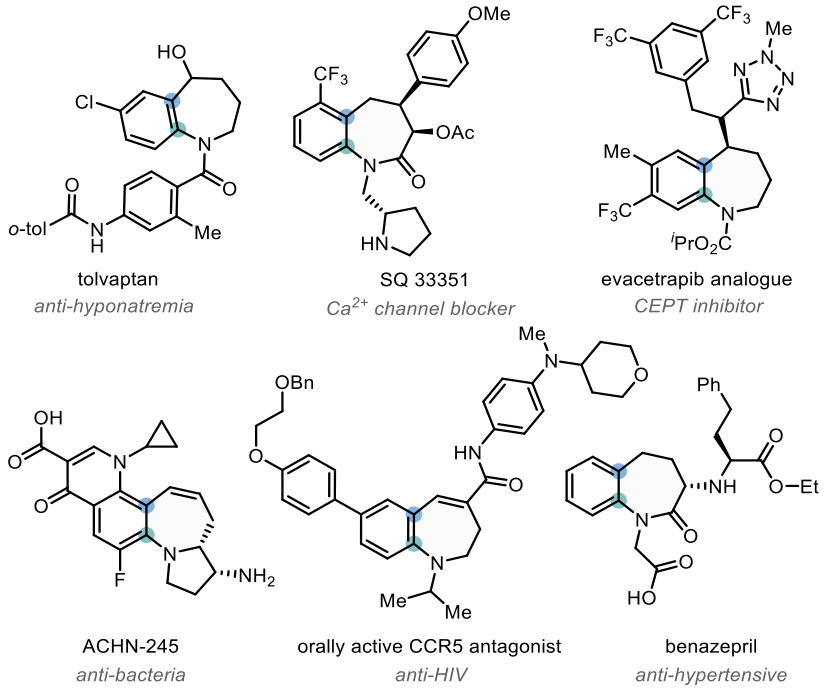
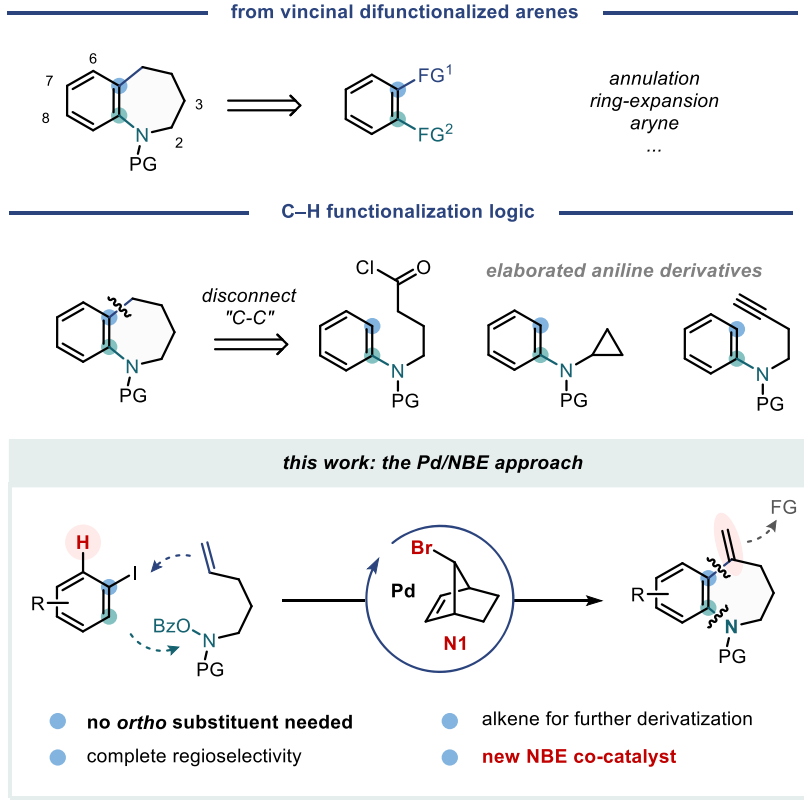


Figure 1. Examples of tetrahydrobenzo[*b*]azepine (THBA)-based bioactive compounds.

Scheme 1. Synthetic Strategies toward THBAs[a]



[a]PG, protecting group; FG, functional group.

NBE-catalyzed annulations require the presence of an ortho substituent on the aryl iodide substrate[16] in order to promote the desired NBE extrusion. Without ortho substituents, di-ortho amination and formation of NBE-attached side-products can dominate,[15c] leading to low yield and low selectivity. Thus, this so-called "ortho constraint"[17] represents a major limitation to this method, as such ortho substituents are unnecessary in most bioactive THBAs (e.g., in Figure 1). Second, most ortho aminations employ cyclic amine electrophiles;[14,18] in contrast, acyclic ones (i.e., those needed for THBA synthesis) are

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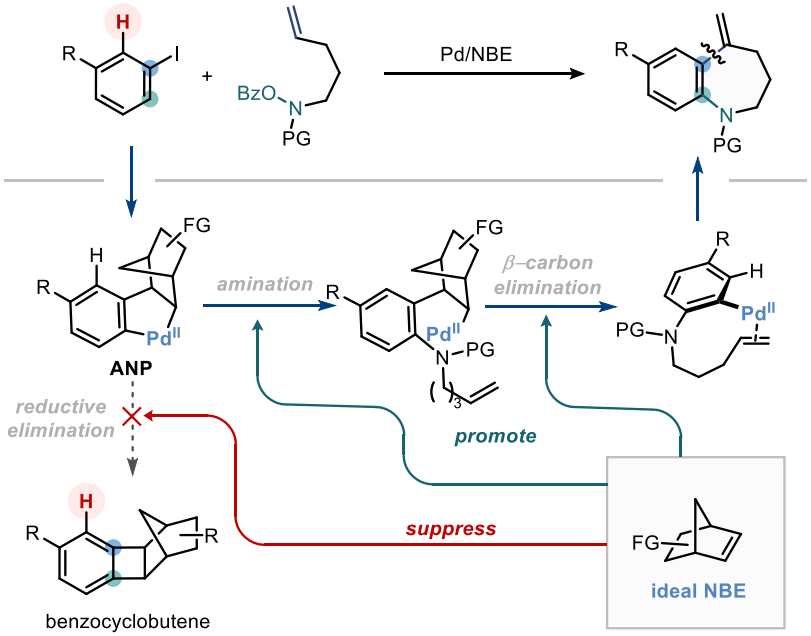
Scheme 2. Challenges of Synthesizing THBAs from Ortho-Unsubstituted Aryl Iodides



relatively bulkier and generally less reactive because of the steric requirement when reacting with ANP.[19] The slow reaction between ANP and the electrophile can lead to competing ANP reductive elimination to generate the benzocyclobutene side product. Third, comparing to five- or six-membered ring formation, it is uncommon to use the tethered electrophile/nucleophile approach to construct medium-sized rings via the Pd/NBE catalysis.[20] This issue could be more prominent for the ortho-unsubstituted substrates, as the enhanced barrier of the NBE exclusion step can further hinder the kinetically less favorable ipso-cyclization. As NBE is involved in all the key intermediates, it is therefore expected to play a critical role in overcoming the above difficulties. Thus, the "ideal NBE" cocatalyst in this scenario needs to efficiently promote the *β*-carbon elimination to address the "ortho constraint", inhibit ANP reductive elimination to avoid the benzocyclobutene side-product, and not hinder the reaction between ANP and the bulky amine electrophile. To the best of our knowledge, a NBE cocatalyst exhibiting all these features has not been reported. In this article, we describe a full story of discovering a unique C7-bromo-substituted NBE (**N1**) that effectively addresses the aforementioned three challenges to realize general THBA synthesis. The unique and versatile roles of the bromo substituent of **N1** in this catalysis have also been disclosed in this study.

RESULTS AND DISCUSSION

To explore this strategy, we chose as 1-chloro-3-iodobenzene (**1a**) as the initial substrate because of its relevance to the synthesis of drug tolvaptan (vide infra, Scheme 3). *O*-Benzoyl hydroxylamine **2a** containing a terminal alkene was prepared in two steps from commercially available chemicals and employed as the initial coupling reagent; *para*-methoxylbenzyl (PMB) was used as the nitrogen-protecting group because of the ease of its removal. Not surprisingly, the initial trials with simple NBE (**N2**) only afforded a complex mixture with NBE-containing side products (see the Supporting Information). The C1-substituted NBE, known to enable mono ortho functionalization of ortho-

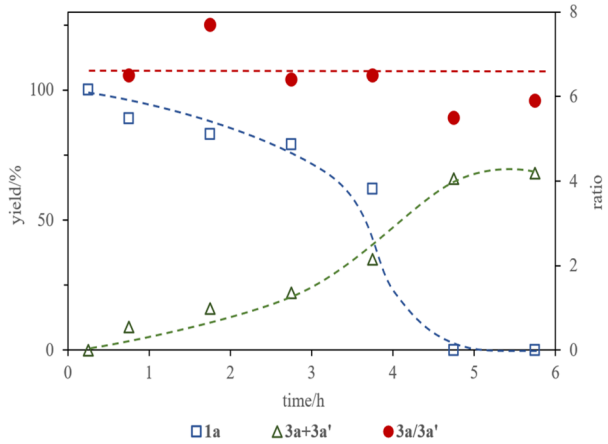


Figure 2. Kinetic profiles for the model reaction and ratio of products over time.

unsubstituted aryl halides with unhindered electrophiles,[17] was found to be ineffective, with the formation of a large amount of the benzocyclobutene side product (for detailed discussions, see the Study of the NBE Effect and Scheme 5). After an extensive screening of various structurally modified NBEs,[21] to our surprise, 7-bromosubstituted NBE (**N1**) proved to be optimal and efficient for this challenging THBA synthesis (Table 1, entry 1). For comparison, NBEs with substitutions at other positions (**N3**–**N9**) all gave low yield and low selectivity (vide infra) in this reaction (entry 2). Notably, C7-substituted NBEs have not been used as the optimal NBE in any previous Catellani-type reactions, likely due to the concern of the C7 sterics on the NBE exo-face where the Pd migratory insertion normally takes place. The bromine group also appears to be important, as replacing Br with an alkoxy group (**N10**), an iodo group (**N11**), or a chloro group (**N12**) led to a significant drop of the yield (vide infra). The anti-7-bromonorbornene (**N13**) also gave a much inferior result, which indicated that the inductive effect of the Br may not be responsible for the high efficiency of **N1**. The less sterically hindered and more *π*-acidic phosphafluorene (**L1**)[22] was found

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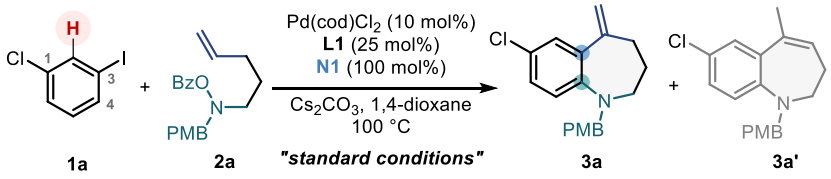
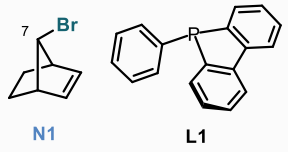
Table 1. Control Experiments



1a 2a 3a 3a'

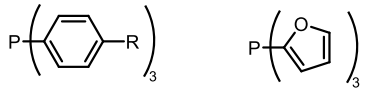
Entry[a]	Variations from the "standard conditions"	Yield (%) [b]	3a/3a' [b]
1	none	72	5.9 : 1
2	other norbornenes instead of **N1**		listed below
3	other ligands instead of **L1**		listed below
4	No Pd	0	
5	No **N1**	0	
6	No **L1**	0	
7	$Pd(OAc)_2$ instead of $Pd(cod)Cl_2$	29	5.6 : 1
8	CsOAc instead of Cs_2CO_3	5	
9	K_2CO_3 instead of Cs_2CO_3	6	
10	**N1** (50 mol%)	55	5.5 : 1
11	**N1** (25 mol%)	49	5.1 : 1

co-catalyst and ligand



N1 L1

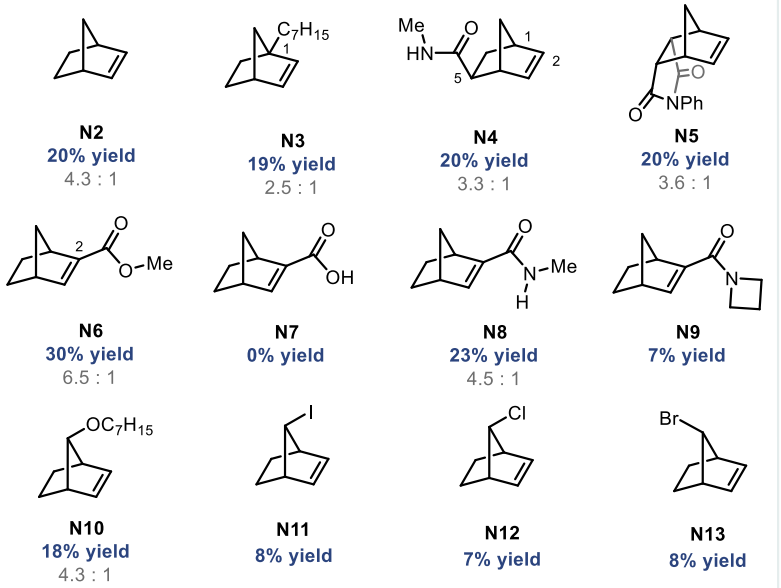
ligand effect



R = H, **L2**, 7%
R = OMe, **L3**, 7%
R = CF_3, **L4**, 24% (2.0:1)

L5, 54%, (2.0 : 1)

NBE effect



N2 20% yield 4.3 : 1
N3 19% yield 2.5 : 1
N4 20% yield 3.3 : 1
N5 20% yield 3.6 : 1
N6 30% yield 6.5 : 1
N7 0% yield
N8 23% yield 4.5 : 1
N9 7% yield
N10 18% yield 4.3 : 1
N11 8% yield
N12 7% yield
N13 8% yield

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(cod)Cl_2$ (0.01 mmol), ligand (0.025 mmol), NBE (0.1 mmol), and Cs_2CO_3 (0.25 mmol) in 1,4-dioxane (1 mL), 100 °C, 12 h. [b]Yields (**3a** + **3a'**) and ratios were determined by crude ^1H NMR analysis using pyrazine as the internal standard.

to be the best ligand. A survey of the phosphine effect[13] (entry 3 and the Supporting Information) shows that, in general, electron-deficient ligands worked better than electron-rich ones; for example, $P(4\text{-}CF_3C_6H_4)_3$ (**L4**) gave higher yield than $P(4\text{-}OMeC_6H_4)_3$ (**L3**), which was the previously optimal ligand for ortho amination (entry 3).[14a] As expected, the palladium catalyst, phosphine ligand, and NBE were all essential for this transformation (entries 4–6). Similar to our previous findings, $Pd(OAc)_2$ is a worse precatalyst in the context of "ortho constraint" than $Pd(cod)Cl_2$ (entry 7).[17] This is

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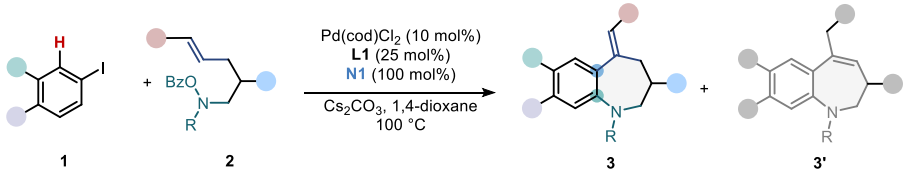
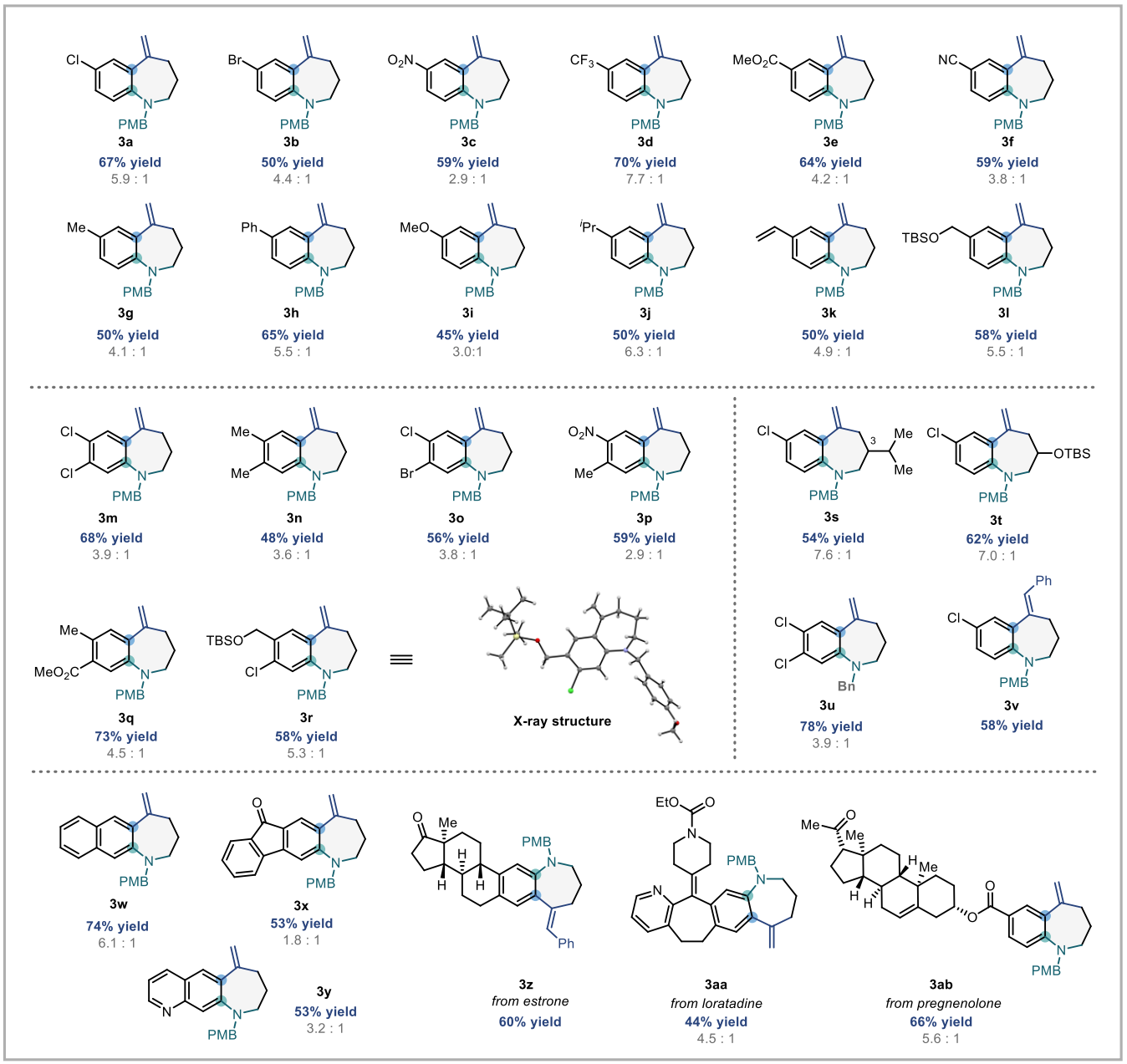
Table 2. Substrate Scope with Ortho-Unsubstituted Aryl Iodides[a]





[a]Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Pd(cod)Cl_2 (0.01 mmol), **L1** (0.025 mmol), **N1** (0.1 mmol), and Cs_2CO_3 (0.25 mmol) in 1,4-dioxane (1 mL), 100 °C, 12 h. All yields are combined isolated yields of the products. The ratios were determined by ^{1}H NMR analysis of crude samples using pyrazine as the internal standard.

presumably due to the noninnocent role of acetate anion in facilitating undesired C−H activation, as the use of cesium acetate as the base almost shut down the reaction (entry 8). In addition, cesium carbonate proved to be a much better base than potassium carbonate (entry 9). Reducing the **N1** NBE loading to 50 and 25 mol % diminished the yield from 72 to 55 and 49%, respectively (entries 10 and 11), though turnover of **N1** can be observed. It is worth mentioning that 71% of **N1** can be recovered under the standard condition. The reaction is regioselective with the annulation only at the C3 and C4 positions (**3a**). The alkene-isomerized product (**3a′**) was formed as a minor product, which can be separated from the main product. The kinetic monitoring of the reaction (Figure 2) shows that **3a′** was generated at the beginning of the reaction

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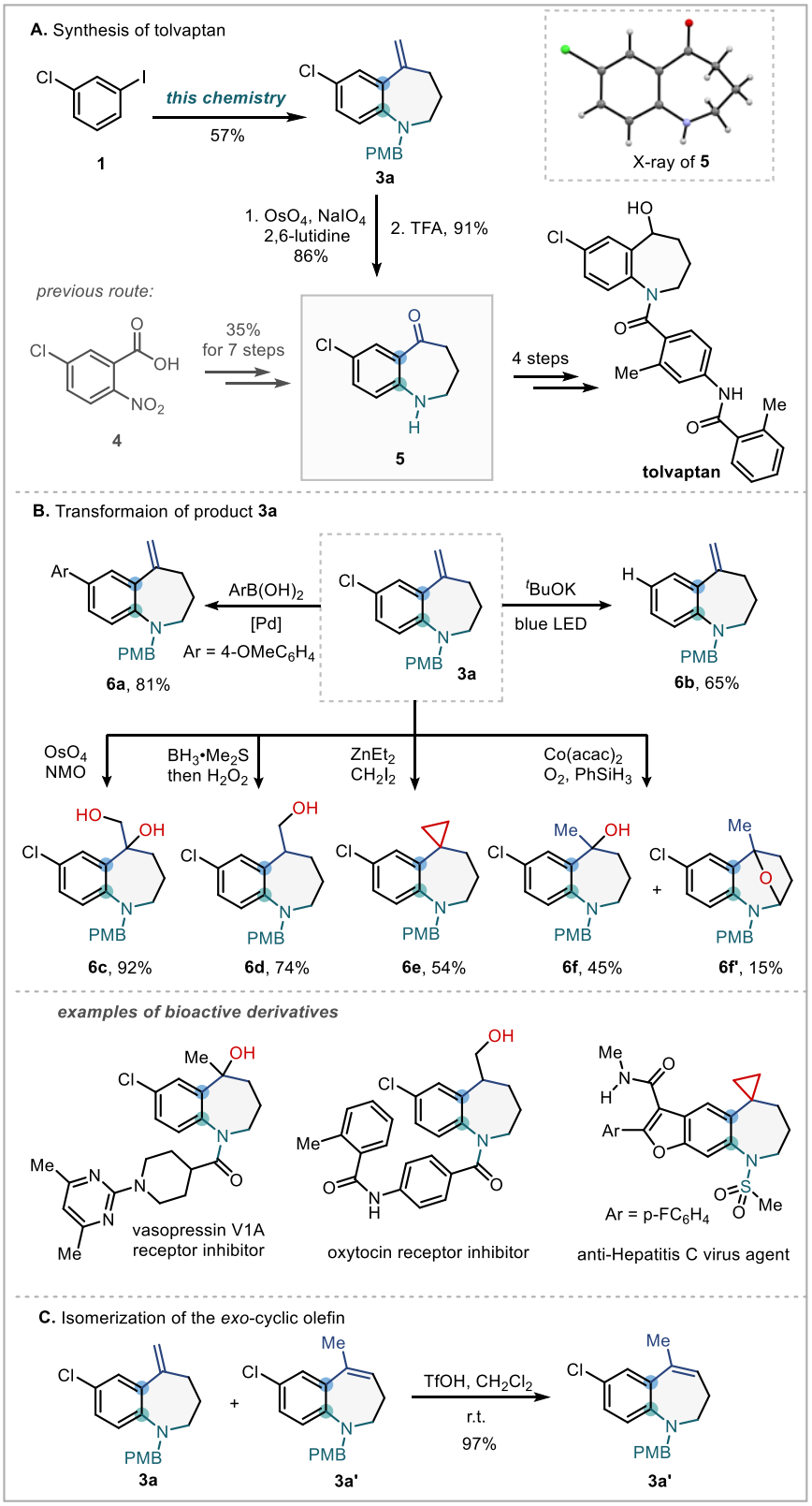
Scheme 3. Synthetic Applications[a]



[a]NMO: *N*-methylmorpholine-*N*-oxide.

and the ratio between **3a** and **3a′** did not change much throughout the reaction. It is likely that the lack of the ortho substituent allows the Pd-hydride reinsertion to generate a tertiary alkyl-Pd(II) species, which can undergo inward *β*-hydrogen elimination to give trisubstituted alkene **3a′**; in sharp contrast, such alkene isomers were not observed with ortho-substituted aryl iodides (vide infra, Table 3), highlighting another challenge with ortho-unsubstituted substrates.

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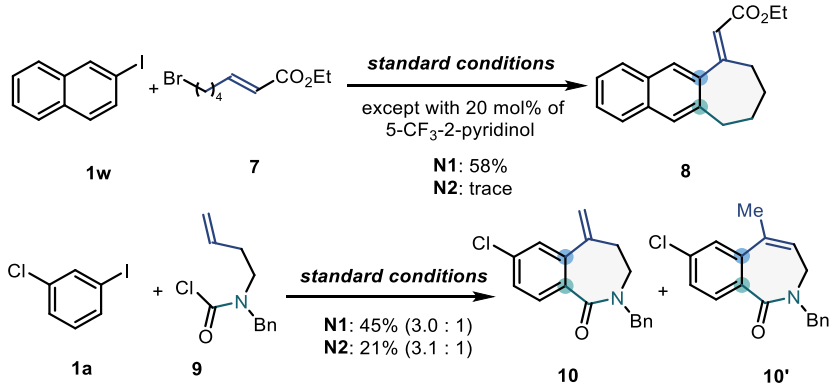
Scheme 4. Extension of the Reaction Scope to Other Types of Ortho Functionalization

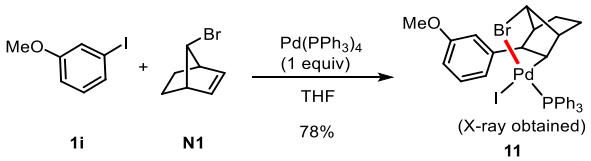


With the optimized conditions in hand, the scope of the THBA formation with ortho-unsubstituted aryl iodides was then examined (Table 2). Both electron-deficient and -rich aryl iodides are competent coupling partners (**3a**−**3l**), though the electron-deficient aryl iodides gave slightly better yields. Besides meta-substituted aryl iodides, meta-, para-disubstituted ones also reacted smoothly (**3m**−**3r**).[23] The reaction conditions can tolerate a wide range of functional groups, including chloro (**3a**), bromo (**3b**), nitro (**3c**), trifluoromethyl (**3d**), ester (**3e**), nitrile (**3f**), terminal alkene (**3k**), and silyl ether (**3l**). Other alkene-tethered *O*-benzoyl hydroxylamines **2** were explored next. When substituted amination reagents were employed, 3-substituted THBAs (**3s**−**3t**) can still be afforded in good yields. Besides the PMB protecting group, simple benzyl can be introduced in even higher yield (**3u**). When using the styrene-tethered reagent, complete selectivity of a single alkene geometrical isomer (**3v**) was observed. It is likely that the conjugation and/or the increased sterics inhibited the alkene isomerization. Finally, *ortho*-unsubstituted aryl iodides derived from naphthalene (**3w**), fluorenone (**3x**), quinoline (**3y**), estrone (**3z**), and loratadine (**3aa**) all delivered the desired THBAs in moderate to good yields. These polycyclic ring-fused azepines with diverse functional groups could be challenging to access via conventional approaches.

Synthetic applications. The utility of this method was then evaluated. Tolvaptan, an aquaretic drug that functions as an orally active vasopressin receptor 2 antagonist, has been used to treat hyponatremia and autosomal dominant polycystic kidney disease. The ketone intermediate **5** was previously prepared in seven steps;[2] for comparison, it can now be accessed in two steps from THBA **3a** (Scheme 3 A). Note that the PMB protecting group can be removed in high yield by treatment with TFA. Due to the modularity of the synthesis, this approach could be beneficial for preparing diverse tolvaptan analogues from readily available substituted aryl iodides. In addition, the chloro group on THBA **3a** can serve as a handle to conveniently introduce other functional groups, e.g., an aryl group (**6a**), via cross couplings (Scheme 3 B); it can also be deleted through reduction (**6b**).[24] Moreover, the alkene moiety in THBA products can undergo dihydroxylation, hydroboration−oxidation, and Simmons−Smith reaction to install vicinal diol (**6c**), primary alcohol (**6d**), and cyclopropane (**6e**), respectively. Furthermore, under the Mukaiyama hydration conditions, the alkene was converted into a tertiary alcohol (**6f**) and an interesting *oxa*-bridged benzazepine (**6f′**). It is noteworthy that these derivatizations could find their relevance in a number of THBA-containing bioactive compounds,[25] implying the versatile role of the alkene moiety for potential medicinal chemistry applications. Finally, under acidic conditions, the mixture of exo- and endo-cyclic products could be isomerized into the thermodynamically more stable internal olefin in nearly quantitative yield (Scheme 3C).

To explore the generality of **N1** in promoting seven-membered-ring formation with ortho-unsubstituted iodoarenes, we examined two other ortho functionalization tactics (Scheme 4). To our delight, besides ortho amination, preliminary success has been achieved with Catellani annulations via ortho alkylation[13] and ortho aminocarbonylation[26] to give benzoannulene and benzoazepin-1-one products, respectively. In contrast, unsubstituted NBE (**N2**) gave much inferior results along with forming a significant amount of NBE-containing side-products, further confirming that the C7-bromo group is critical to addressing the "ortho constraint" and inhibiting undesired pathways.

X-ray Crystal Structure of Complex 11. The unique property of the C7-bromo NBE (**N1**) prompted us to investigate its exact role in the catalysis. Migratory insertion with NBEs typically occurs in a cis, exo manner because of the predistortion of the NBE π bond.[12a,27] However, one cannot assume, a priori, that **N1** should maintain the exo selectivity because of the potential steric repulsion between the C7 substituent with the Pd during the migratory insertion process. To confirm the alkene facial selectivity of the migratory insertion step, we synthesized pure palladium complex **11** in good yield by reacting 3-iodoanisole with **N1** and stoichiometric $Pd(PPh_3)_4$ in anhydrous THF at 90 °C (eq 1). Crystals suitable for X-ray



(1)

analysis were obtained from dissolving **11** in CH_2Cl_2 followed by the addition of MeOH.The X-ray structure of complex **11** clearly shows that the aryl ring and the palladium still remain positioned cis and exo to the norbornyl group (Figure 3, left). Interestingly, the d^8 Pd center possesses a square-planar geometry with PPh_3, iodide, norbornyl group, and the bromo substituent. This is in contrast with the literature reported analogue (complex **12**)[28] with simple NBE, where the η^2 coordination with the C(5)−C(6) π bond occupies one of the four coordination sites (Figure 3, right). Other bond lengths, such as Pd(1)−I(2), Pd(1)−C(3), and Pd(1)−P(4) bonds, remain largely unchanged. Such

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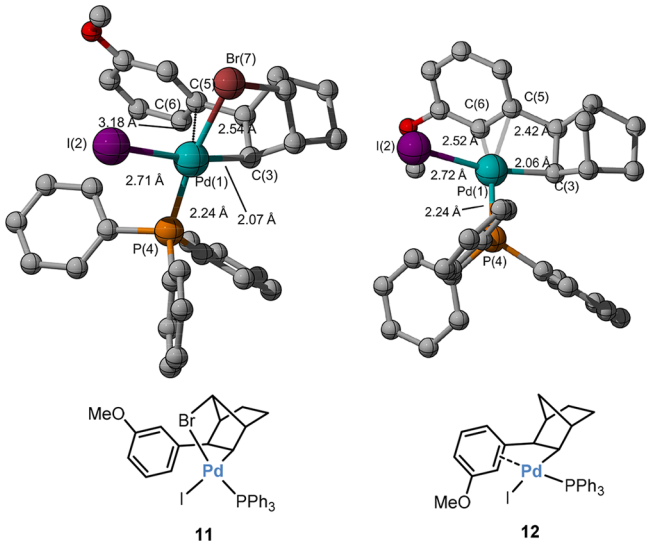
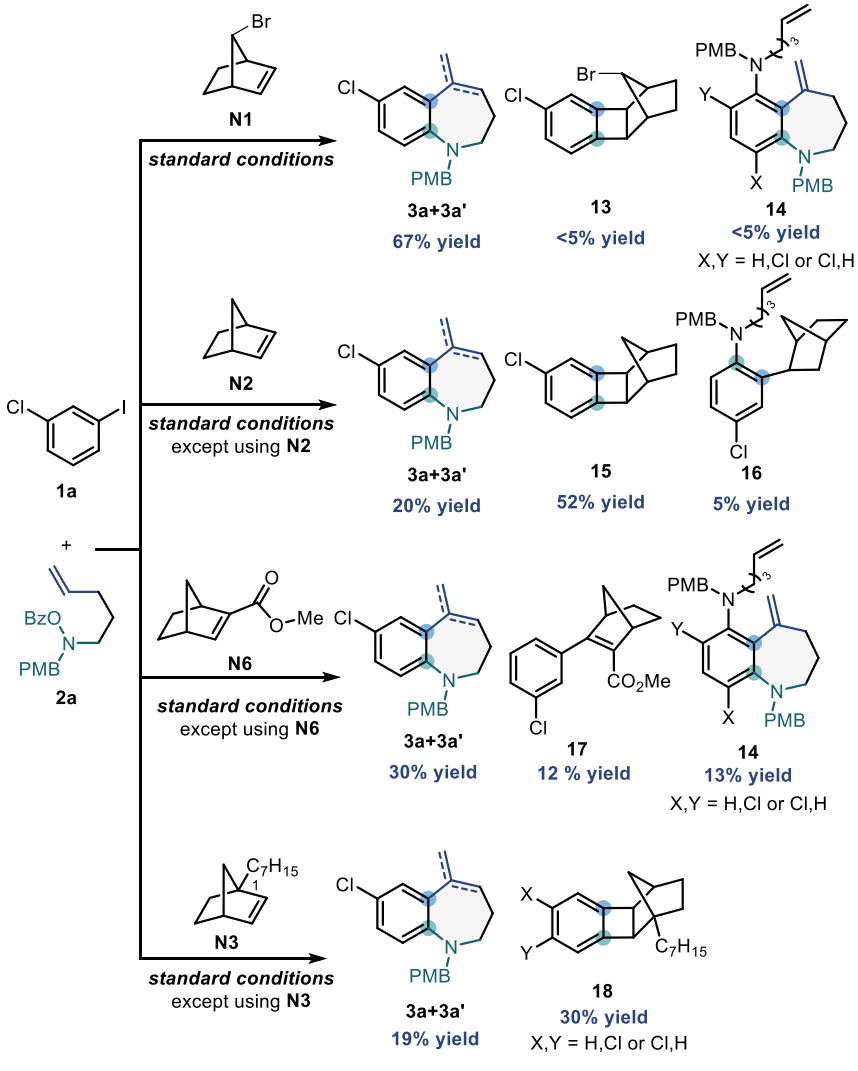


Figure 3. Structures of complex **11** and **12** (ref 28) as determined by X-ray crystallography.

a weakly coordinating bromo substituent can be considered as a "built-in" L-type ligand into NBE, which may have some implications in catalysis (vide infra).

Study of the NBE Effect. To understand the specific role of the C7-bromo substituent, it would be important to first recognize the reactivity differences between different NBEs. As such, side products of the model reactions with four representative NBEs have been carefully characterized and analyzed (Scheme 5). In contrast to the result with **N1**, benzocyclobutene **15** was the major isolated side-product when simple NBE **N2** was employed. Comparing to the standard ortho amination with cyclic amine electrophiles,[14a] it is likely that the bulkiness of electrophile **2a** or the coordination of the alkene moiety hindered amination with the ANP intermediate. In addition, a minor side product **16** containing the norbornyl group at the ipso position was also isolated, and such a C−H reductive elimination product was not observed when **N1** was used.[29] These results indicated that the bromo substituent in **N1** should also promote β-carbon elimination or prevent C−H reductive elimination. As a comparison, although the sterics of the C2-substituted NBE (**N6**)[30] can effectively inhibit the benzocyclobutene formation,[31] it led to NBE-attached side-product **17** and bis ortho-amination side-product **14**. The

Scheme 5. Isolation of Side Products with Different NBEs



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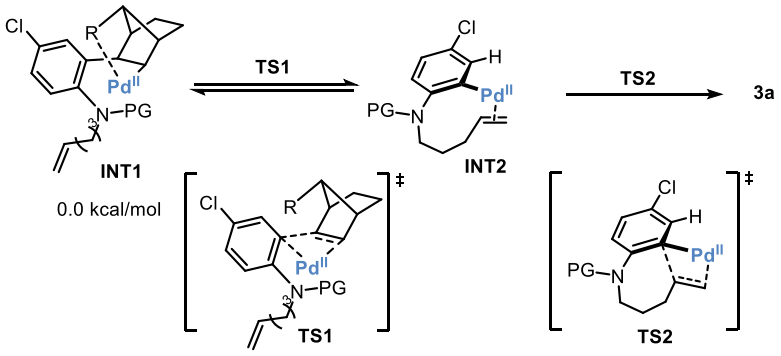

	TS1	INT2	TS2
N2 (R = H)	20.6	11.7	25.3
N1 (R = Br)	21.7	9.0	22.6

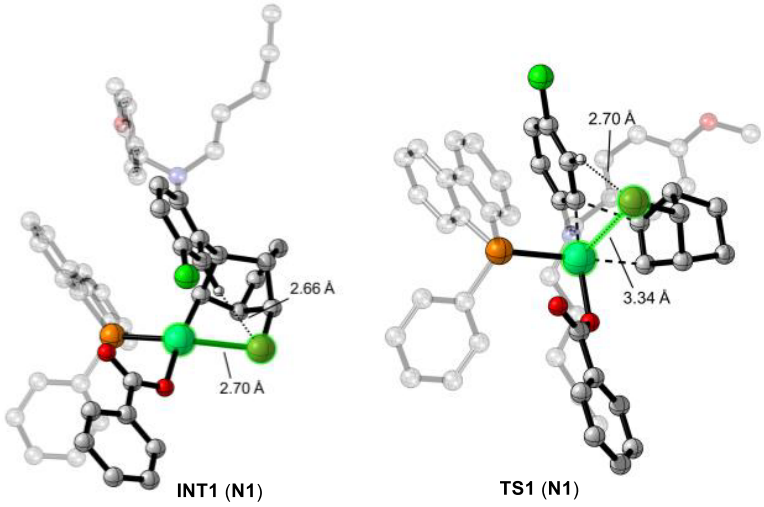

Figure 4. Comparison of the β-carbon elimination and subsequent 7-exo-trig between NBEs **N1** and **N2**. All energies are in kcal/mol. Calculations were performed at the B3LYP-D3/SDD-6-311+G(d,p)-SMD(1,4-dioxane)//B3LYP/LANL2DZ-6-31G(d) level of theory.

formation of **17** is possibly due to the lability of the Pd-enolate intermediate that can undergo protonation or β-hydrogen elimination via the "face switch".[32] The formation of **14** indicates that **N6** cannot efficiently suppress the "ortho constraint". On the other hand, with the C1-substituted NBE (**N3**), no ortho difunctionalized products (like **14**) were observed, showing that **N3** is indeed effective to minimize the second ortho C−H activation. However, direct reductive elimination of ANP became the major side reaction, resulting in undesired benzocyclobutene **18**; compared to **N1**, the increased sterics in the **N3**-derived ANP intermediate renders it less reactive with the bulky electrophile. With **N1** as the cocatalyst, side products (**13** and **14**) were observed with only <5% yields; therefore, the benefits of using the C7-bromo NBE (**N1**) include suppressing ANP reductive elimination, promoting NBE exclusion, and/or inhibiting the second ortho C−H activation without significantly interfering with the reaction between the ANP and the electrophile.

To further elucidate the detailed roles of the bromo moiety of **N1** in this reaction, DFT calculation was conducted. First, the effect of **N1** on the β-carbon elimination and subsequent 7-exo-trig processes was examined (Figure 4). As the 7-exo-trig has a slightly higher barrier than the β-carbon elimination in this reaction, NBE extrusion can be regarded as a pre-equilibrium. The steric repulsion between the bromo substituent and the ortho C−H bond (H···Br distance is 2.66 Å) is expected to account for the faster 7-exo-trig (22.6 with **N1** vs 25.3 kcal/mol with **N2**) by driving the NBE extrusion pre-equilibrium. Another feature of the bromo-substituted NBE is the weak coordination between the Pd and the Br, which was also observed in the X-ray structure of complex **11**. Such weak coordination could stabilize intermediate **INT1** and prevent competing side reactions (e.g., C−H reductive elimination, protonation or β-H elimination). On the other hand, even from a relatively stable intermediate (**INT1**), the β-carbon elimination with **N1** still takes place with a relatively low kinetic barrier. Analysis of the transition state **TS1** (with **N1**) revealed that a weak interaction between the Pd and the Br still exists (Pd···Br distance is 3.34 Å) during the β-carbon elimination transition state. Thus, the kinetic barrier of the β-carbon elimination remains very similar to simple NBE **N2** (21.7 vs 20.6 kcal/mol). As a result, the DFT study implies that the overall NBE extrusion and subsequent Heck cyclization process is more favorable with **N1**.

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J. Am. Chem. Soc. 2021, 143, 9991−10004

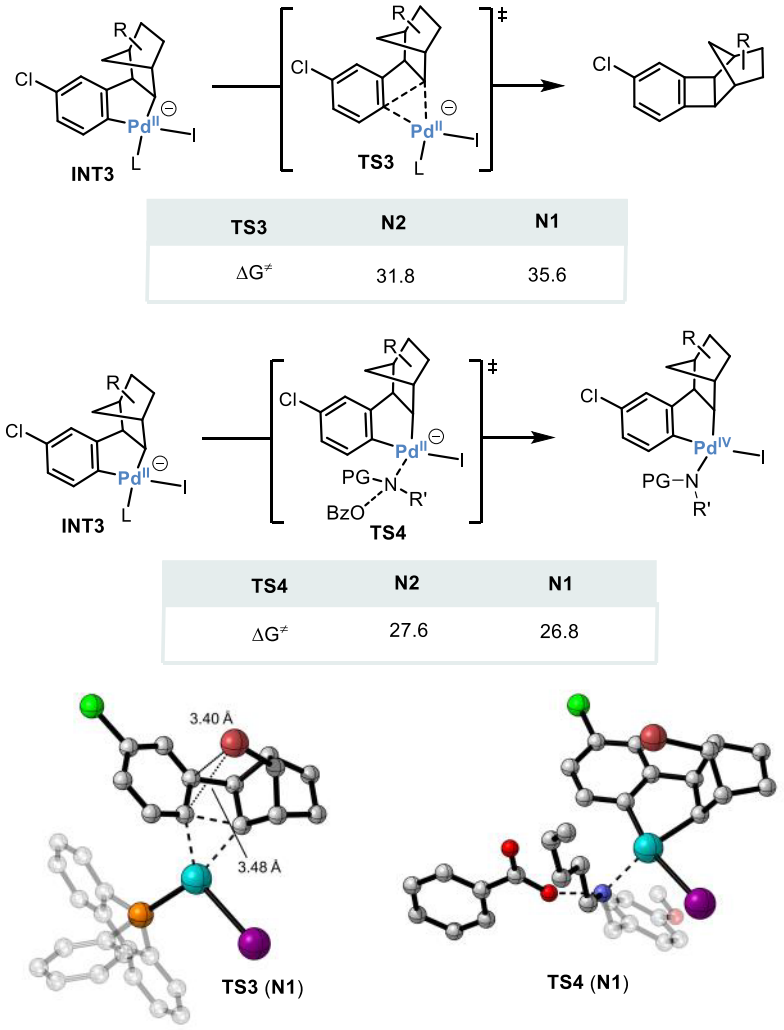

Figure 5. Comparison of reductive elimination from **INT3** between NBE **N1** and **N2**. All energies are in kcal/mol.

Meanwhile, the reactivity differences between **N1**- and **N2**-derived ANPs (**INT3**) have also been studied computationally (Figure 5). The benzocyclobutene side products (e.g., **15** and **18**) have been previously found to come from reductive elimination of the anionic ANP intermediate (**INT3**).[19] Through the DFT calculation, the presence of the electronegative bromo substituent in **N1**-derived ANP was found to disfavor the reductive elimination by 4.3 kcal/mol relative to the one derived from **N2**. The increased kinetic barrier was presumably due to the repulsive interaction between the negatively charged Br atom with the arene π electrons in **TS3**. This is evidenced by the shortest C···Br bond distance of 3.40 Å (the sum of their van der Waals radii is 3.55 Å) in the required transition state. On the other hand, **INT3** derived from **N1** has a very similar oxidative addition barrier with **2a** to that of **N2**, indicating its reactivity with electrophiles is not affected by the bromo substituent. This could be explained by the fact that the bromo substituent does not have significant steric repulsion with the electrophile during the transition state **TS4** (**N1**) (the shortest H···Br distance is over 4 Å). Thus, the DFT study also supports that NBE **N1** can inhibit the ANP reductive elimination without compromising the reaction with the electrophile.

As a summary of the NBE effect, the C7-bromo-substituted **N1** indeed exhibits a range of unique and versatile features. First, the bromo atom can serve as a built-in L ligand to stabilize reaction intermediates to minimize side reactions. In addition, it can promote NBE extrusion through stabilizing the β-carbon elimination transition state, therefore addressing the "ortho constraint" challenge. Moreover, the electronegative Br substituent can suppress ANP reductive elimination because of charge repulsion with the metalated arene. Finally, the lack of steric bulkiness of the Br substituent retains good reactivity of the ANP with the electrophile. Altogether, the C7-bromo-substituted **N1** is well suited for the challenging medium-sized-ring formation with ortho-unsubstituted aryl iodides.

Scope of the Ortho-Substituted Aryl Iodides. Finally, to complete the method development for the Pd/NBE-catalyzed THBA synthesis, we also investigated the scope of using ortho-substituted aryl iodides (Table 3). Aided by the ortho substituents, this reaction can now be achieved in good yields by several NBEs (see the Supporting Information for details), with the C2-substituted[30] NBE **N14** being optimal.[33] In addition, without the challenge of the "ortho constraint", the use of acetate salts (e.g., CsOAc and $Pd(OAc)_2$) was beneficial, possibly through promoting the concerted metalation deprotonation during the C−H activation step. The reaction can also

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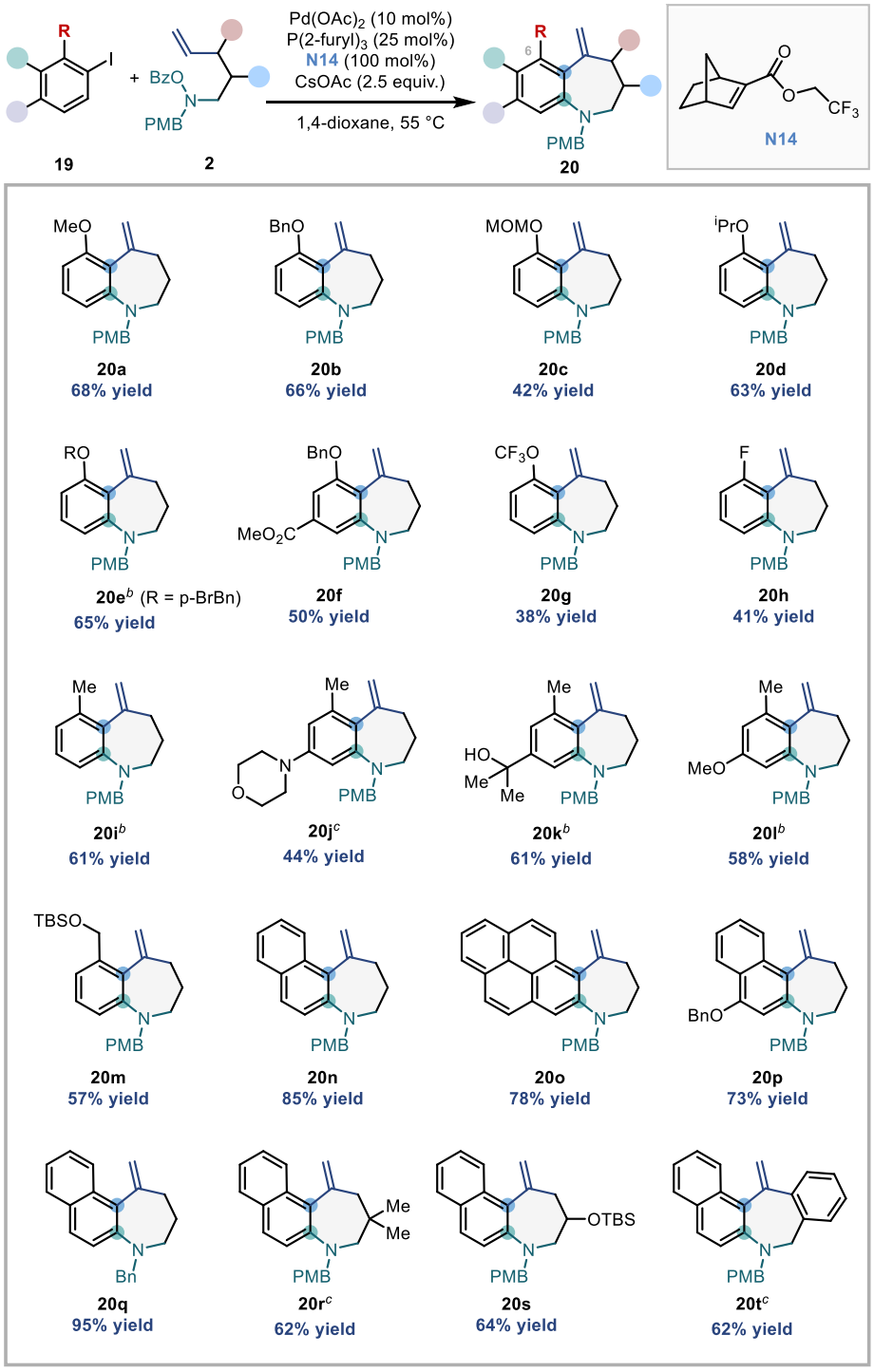
J. Am. Chem. Soc. 2021, 143, 9991−10004

Table 3. Substrate Scope of the Ortho-Substituted Aryl Iodides[a]



[a]Reaction conditions: **19** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), $P(2\text{-furyl})_3$ (0.025 mmol), **N14** (0.1 mmol), CsOAc (0.25 mmol) in 1,4-dioxane (1 mL), 55 °C, 45 h. [b]70 °C, 18 h. [c]100 °C, 12 h.

proceed at a lower temperature. No obvious alkene isomerization was observed (vide supra). It is likely that the bulkiness of the ortho substituents inhibits the palladium-hydride reinsertion. Moreover, a number of different ortho substituents with various steric and electronic properties were tolerated. Similarly, the high chemoselectivity and broad functional group/linker compatibility make this method generally able to access diverse C6-substituted THBAs.

CONCLUSION

In summary, a unique C7-bromo-substituted NBE **N1** has been identified to be an "ideal" cocatalyst in promoting THBA and other seven-membered ring synthesis from ortho-unsubstituted aryl iodides. The broad substrate scope, the high functional group tolerance, and the synthetic versatility of the alkene functionality should make this method attractive for modular preparation of substituted THBAs. The knowledge gained on

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J. Am. Chem. Soc. 2021, 143, 9991−10004

the distinct and versatile roles of the C7-bromo group in **N1** could have implications on new catalyst design. Further investigations of **N1** (and its analogues) in promoting other challenging Catellani-type transformations are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04575.

Detailed experimental procedure, ^{1}H NMR and ^{13}C NMR spectra, and DFT studies (PDF)

Accession Codes

CCDC 2055263 and 2079773−2079774 contain the supplementary crystallographic data for this paper. These 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, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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(33) The C7-bromo NBE **N1** can also give good yields with ortho-substituted aryl iodides. For details, see the Supporting Information.

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J. Am. Chem. Soc. 2021, 143, 9991−10004