Published in final edited form as:
Org Lett. 2010 March 5; 12(5): 1028–1031. doi:10.1021/ol100033s.

Synthesis of Polycyclic Nitrogen Heterocycles via Alkene Aminopalladation/Carbopalladation Cascade Reactions

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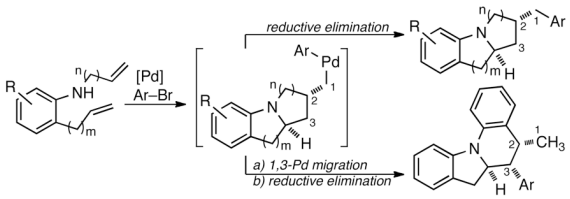
Abstract



A new method for the synthesis of tricyclic nitrogen heterocycles from *N*,2-diallylaniline derivatives is described. These transformations proceed via sequential alkene aminopalladation of an intermediate $L_nPd(Ar)(NRR')$ species followed by alkene carbopalladation of the resulting $L_nPd(Ar)(R)$ complex. Both alkene insertion steps occur in preference to C–N or C–C bond-forming reductive elimination. An unusual 1,3-palladium shift occurs when 2-Allyl-*N*-(2-vinylphenyl)aniline is employed as substrate, which yields a tetracyclic molecule with three contiguous stereocenters.

Over the past several years our group has developed a method for the construction of nitrogen heterocycles via Pd-catalyzed carboamination reactions between aryl bromides and amines bearing pendant alkenes.[1] For example, treatment of an *N*-substituted 2-allylaniline derivative (e.g., **1**) with an aryl bromide in the presence of NaO*t*Bu and a palladium catalyst leads to the formation of a 2-benzylindoline product (**4**).[2] These reactions proceed via intramolecular alkene aminopalladation of palladium(aryl)(amido) complex **2** to yield **3a**, which undergoes reductive elimination to give **4** (Scheme 1).

It seemed plausible that this method could be extended to cascade cyclization processes that yield tricyclic products if an intermediate related to **3a** could be intercepted with a pendant alkene. For example, if *N*,2-diallylaniline were employed as a substrate, alkene aminopalladation of **2** (R = allyl) would yield **3b**, which could undergo intramolecular carbopalladation to give **5**. Reductive elimination would then yield **6**. Overall, this transformation would generate three bonds, two rings, and two stereocenters in a single step from a simple starting material. Importantly, this method would provide a new means to access benzo-fused 1-azabicyclo[3.3.0]octanes (**6**) and related 1-azabicyclo[4.3.0]nonanes. These scaffolds are a prominent feature of several natural products,[3] and have also served as key intermediates in the synthesis of analogous fully saturated ring systems.4

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Supporting Information Available. Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments with supporting crystallographic structural data, and copies of ^1H and ^{13}C NMR spectra for all new compounds reported in the text (102 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

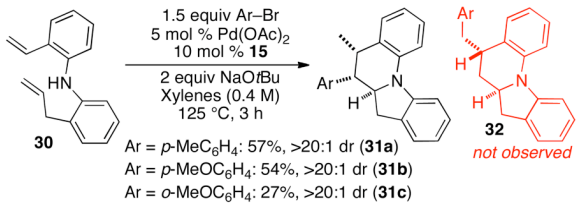
The approach outlined in Scheme 1 sharply contrasts with related palladium-catalyzed cascade Heck reactions between polyalkene substrates bearing pendant alkenyl (or aryl) halides (Scheme 2).[5,6,7] The Heck cascades occur through sequential intramolecular alkene carbopalladation reactions of R-Pd-X intermediates such as **8** or **9** (X = halide or pseudohalide), and are usually terminated by β-hydride elimination from the final R-Pd-X species (**10**) to generate an alkene (**11**). Thus, elements of molecular complexity present in **10** are removed in the terminal step, as the β-elimination leads to loss of a stereocenter and an organometallic functional group. In comparison, the final step of the aminopalladation/carbopalladation cascade shown in Scheme 1 (reductive elimination from **5** to yield **6**) would produce a C–Ar bond, and the stereocenters generated in each alkene insertion step would be retained in the product.[8]

Although the cascade aminopalladation/carbopalladation sequence could have considerable utility, in order to achieve our desired transformation, we would need to overcome a significant obstacle that is not present in the cascade Heck reactions. The key intermediates in the Heck cascades (**8** and **9**) contain only a single C–Pd bond. Thus, premature termination of the cascade via competing reductive elimination from **8** or **9** cannot occur, as C–X bond forming reductive elimination from Pd(II) is thermodynamically unfavorable.[9] *In contrast, intermediate **3b** contains two Pd–C bonds, and can potentially undergo competing irreversible C–C bond-forming reductive elimination to afford undesired monocyclized product **4**.* In addition, the catalyst employed for the cascade cyclization must not only favor alkene insertion over reductive elimination from **3b**, but also must allow the requisite reductive elimination from **5** to proceed.

In our initial experiments we sought to find a catalyst that would facilitate the desired cascade reaction. To this end, we examined the coupling of **1** (R = allyl) with bromobenzene using catalysts generated *in situ* from mixtures of palladium acetate and phosphine ligands (Table 1). As anticipated, these reactions afforded two major products: **12** and **13**.[10] After some exploration, we discovered that bulky triaryl phosphines **14** and **15** provided **12** in acceptable chemical yields and diastereoselectivities.

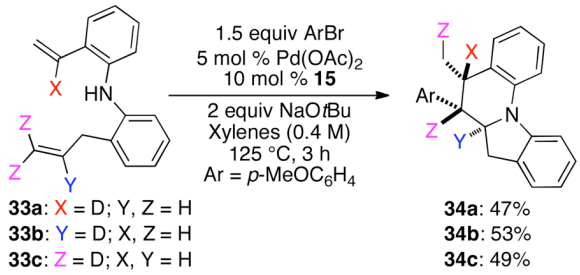
Having discovered a viable catalyst system for the cascade cyclization reaction of **1**, we proceeded to examine analogous transformations of related substrates. As illustrated in Table 2, a number of *N*,2-diallylaniline derivatives (**1**, **16**–**17**) were converted to benzo-fused-1-azabicyclo[3.3.0]octanes **20**–**25** in moderate yields with moderate to good diastereoselectivities. Substitution at the benzylic position was tolerated, as illustrated by the conversion of **18** to **26** and **27**. The conversion of *N*-allyl-2-(but-3-enyl)aniline (**19**) to benzo-fused-1-azabicyclo[4.3.0]nonanes **28**–**29** was also achieved with moderate to good yields and selectivities. However, efforts to transform substrates bearing disubstituted alkenes have been unsuccessful. In addition, the coupling of 2-bromotoluene with **1** afforded monocyclic *N*-allyl-2-(2-methylbenzyl)indoline (**4**, Ar = 2-methylphenyl) as the major product, which was isolated in 72% yield. Only a small amount of the desired bicyclic compound was generated in this reaction.

Although most substrates examined afforded the anticipated products, reactions of **30** with aryl bromides provided surprising results (eq 1). The expected products **32a–c**, were not obtained, but instead 31a–c were generated in moderate yield with excellent diastereoselectivity.



(1)

In order to probe the origin of this unexpected regioisomer, we conducted three experiments with deuterium labeled substrates **33a–c**. As shown in eq 2, substrates **33a** and **33b** were converted to **34a** and **34b**, with no migration of the label observed in either case. In contrast, substrate **33c**, bearing deuterium atoms on the terminal carbon of the allyl group were transformed to **34c** with migration of a deuterium atom to the C5-methyl group.



(2)

On the basis of this data, we suggest that formation of **34c** may proceed as illustrated in Scheme 3. An initial aminopalladation followed by carbopalladation could effect the conversion of **33c** to key intermediate **35** as outlined above (Scheme 1). A surprising and unprecedented 1,3-palladium/hydride shift would then yield **36**, which could undergo reductive elimination to afford **34c**. Although through-space palladium migrations have previously been observed,[11] only a single report has described Pd-migration from one sp^3-hybridized carbon to another.[12] The conversion of **35** to **36** is particularly surprising given the fact that **35** also contains hydrogen atoms that could potentially undergo β-elimination.

In conclusion we have developed a new cascade reaction for the synthesis of polycyclic nitrogen heterocycles that proceeds by way of sequential aminopalladation and carbopalladation. These transformations illustrate that catalyst tuning can allow alkene insertion processes to occur in preference to C–N or C–C bond-forming reductive elimination in $L_nPd(Ar)(NR_2)$ or $L_nPd(Ar)(R)$ complexes. In addition, we have observed the first occurrence of 1,3-palladium migration of an alkylpalladium intermediate. Studies on the scope of this method and the application of these concepts to the development of new catalytic reactions are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the NIH-NIGMS for financial support of this work (GM-071650). Additional funding was provided by GlaxoSmithKline, 3M, Amgen, and Eli Lilly. The authors thank prior Wolfe group member Dr. Josephine S. Nakhla (currently at Sigma-Aldrich) for conducting initial experiments in this area.

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6. For cascade reactions of enynes that proceed through similar intermediates, see: (a) Trost BM, Shi YJ. Am. Chem. Soc 1993;115:9421. (b) Meyer FE, Parsons PJ, de Meijere A. J. Org. Chem 1991;56:6487.
7. For Pd(II)-catalyzed oxidative cascade reactions that generate heterocycles through aminopalladation of L_nPdX_2 alkene complexes followed by alkene carbopalladation, see: Yip K-T, Zhu N-Y, Yang D. Org. Lett 2009;11:1911. [PubMed: 19338292] and references cited therein
8. To the best of our knowledge, only two reports of intermolecular cascade Heck reactions between aryl or alkenyl halides and 1,n-dienes have appeared in the literature. In these cases the transformations were terminated by aryl C-H activation followed by C-C bond formation; all alkene insertion steps proceed through R-Pd-X intermediates. See: (a) Hu Y, Ouyang Y, Qu Y, Hu Q, Yao H. Chem. Commun 2009:4575. (b) Hu Y, Song F, Wu F, Cheng D, Wang S. Chem. Eur. J 2008;14:3110.
9. Roy AH, Hartwig JF. J. Am. Chem. Soc 2001;123:1232. [PubMed: 11456679]
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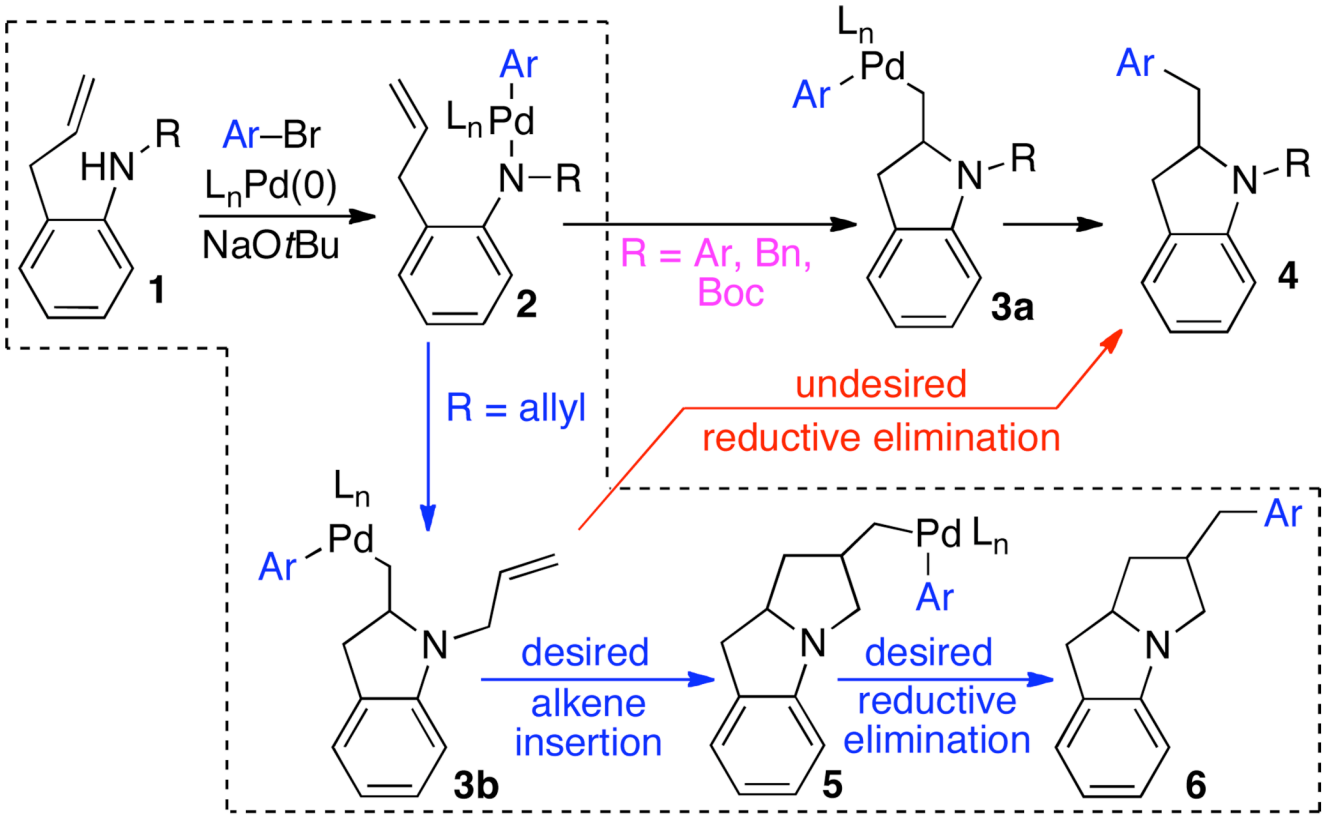
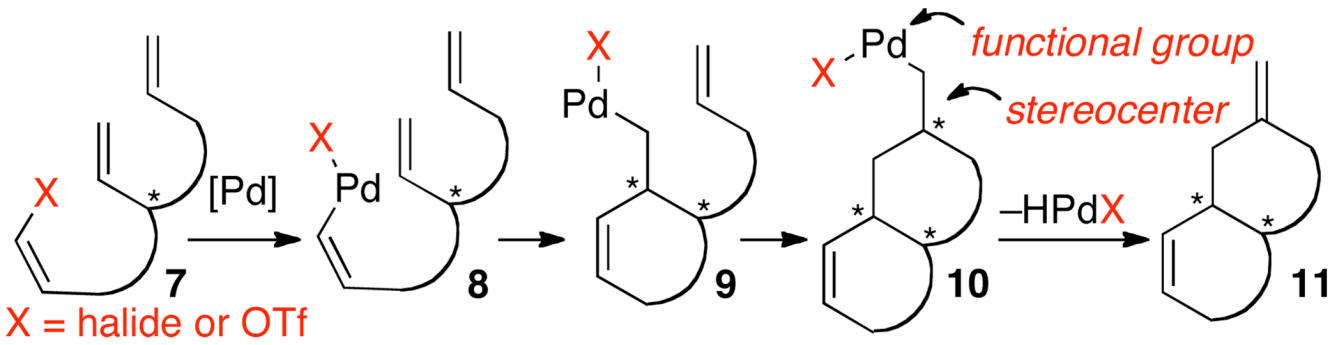
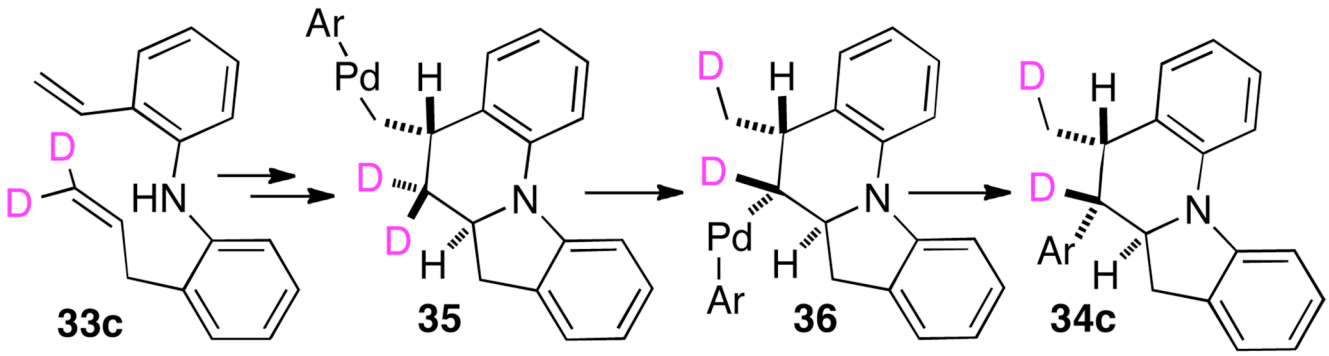


Scheme 1.
Cascade Aminopalladation/Carbopalladation



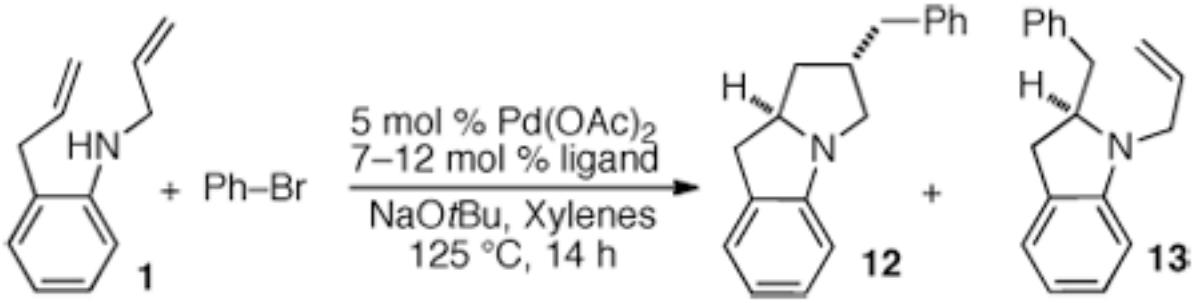
Scheme 2.
Comparison to Cascade Alkene Carbopalladation

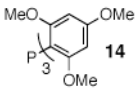
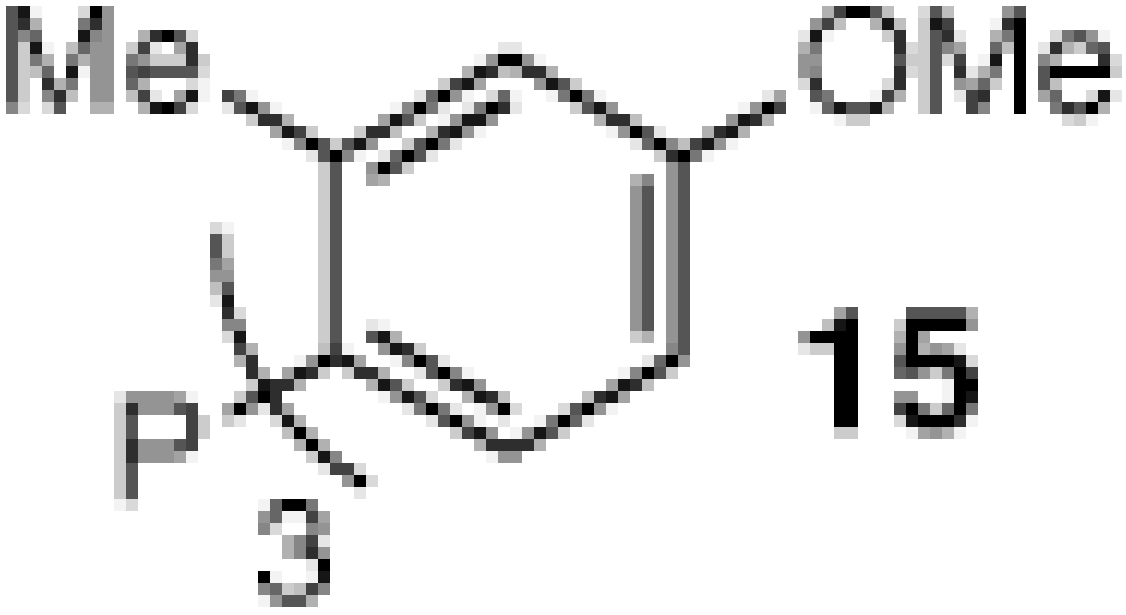


Scheme 3.
Proposed Mechanism for Formation of **34c**

Table 1

Optimization Studies[a]

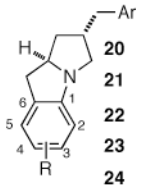


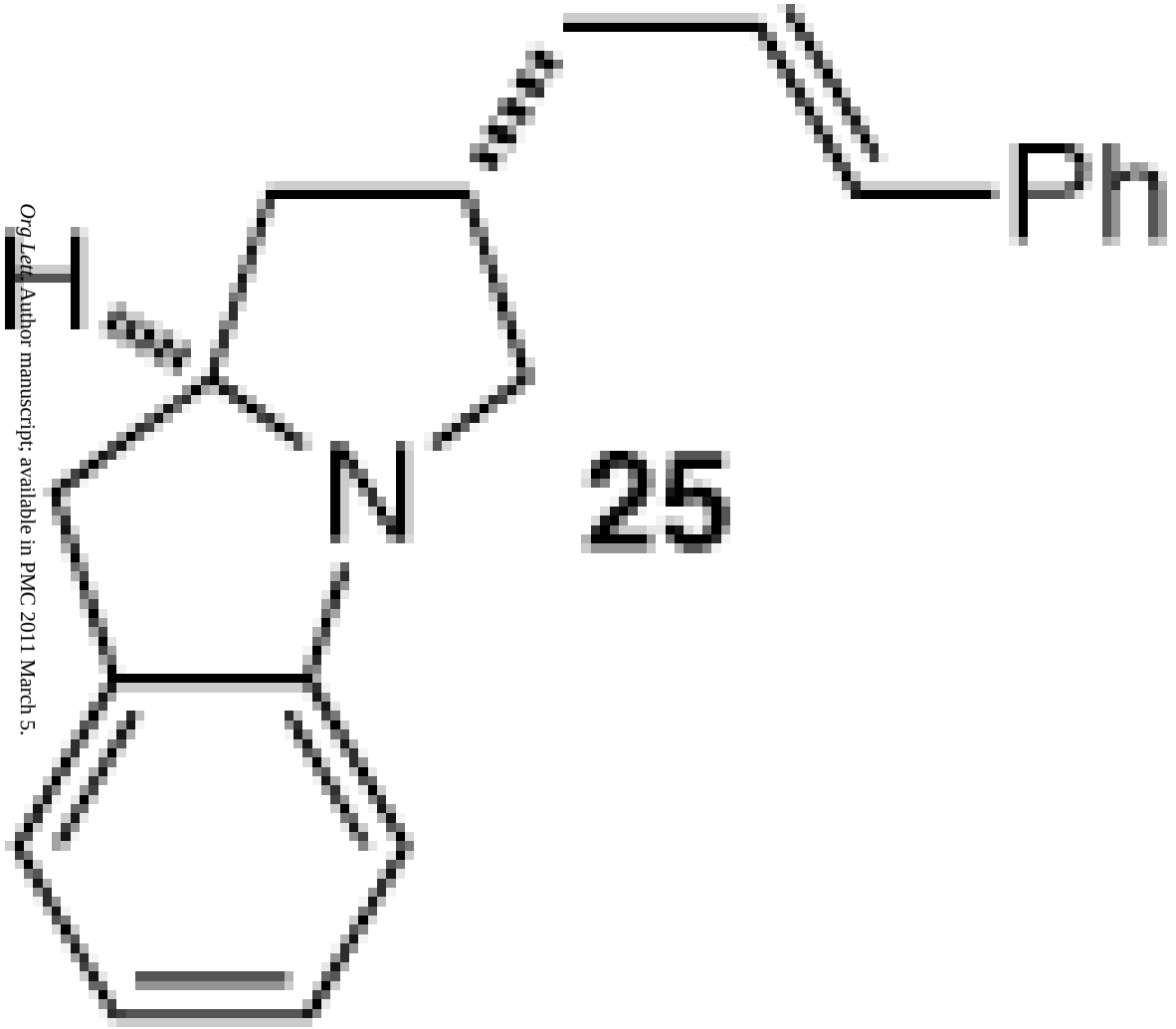
entry	ligand	12:13	dr 12
1	Dpe-phos	2:1	1:1
2	Dppf	2:1	2:1
3	Nixantphos	0:100	–
4	P(*o*-tol)$_3$	3:1	4:1
5	PCy$_3$	2:1	2:1
6	 **14**	6:1	3:1
7	 **15**	5:1	5:1

[a]Conditions: Reactions were conducted on a 0.11 mmol scale using 1.0 equiv **1**, 1.5 equiv PhBr, 1.5 equiv NaO*t*Bu, xylenes (0.2 M), 125 °C, 14 h.

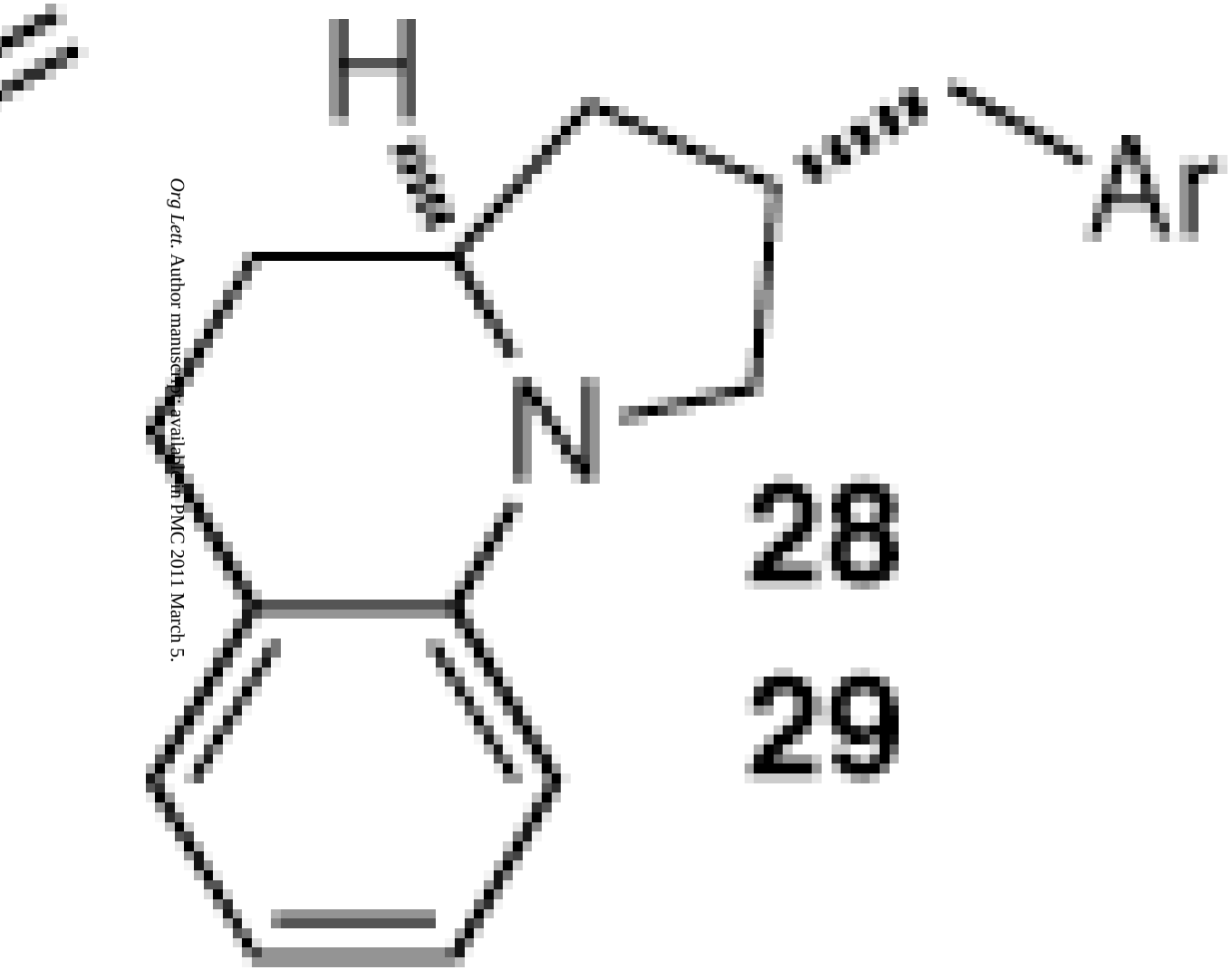
[b] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures that contained phenanthrene as an internal standard. The mass balance of these reaction mixtures was composed of products resulting from β–hydride elimination of intermediate **2**, **3b**, or **5**.

[c] Isolated yield.

product	R	Ar	ratio bicyclic: monocyclic[b]	dr[c]	yield[d]
 **20**	H	*p*-$CF_3C_6H_4$	10:1	>20:1 (5:1)	46%
21	H	*p*-MeC_6H_4	3:1	10:1 (10:1)	66%
22	H	*p*-$MeOC_6H_4$	5:1	13:1 (5:1)	53%
23	3-MeO	*p*-MeC_6H_4	2:1	10:1 (5:1)	57%
24	4-F	*p*-$(Me_2N)C_6H_4$	2:1	7:1 (3:1)	58%

product	R	Ar	ratio bicyclic: monocyclic[b]	dr[c]	yield[d]
			2:1	3:1 (3:1)	42%

product	R	Ar	ratio bicyclic: monocyclic[b]	dr[c]	yield[d]
	Ph	Ph	7:1	18:1 (7:1)	67%
	p-PhC(O)C_6H_4	Ph	7:1	>20:1 (10:1)	68%

product	R	Ar	ratio bicyclic: monocyclic[b]	dr[c]	yield[d]
					
28		Ph	5:1	3:1 (3:1)	70%
29		*p*-$MeOC_6H_4$	5:1	3:1 (3:1)	47%

[a] Conditions: Reactions were conducted on a 0.3–0.5 mmol scale using 1.0 equiv substrate, 1.5 equiv ArBr, 1.5 equiv NaO*t*Bu, xylenes (0.4 M), 125 °C, 14 h.

[b] Ratio of bicyclic product:monocyclic product observed in crude reaction mixtures.

[c] Diastereomeric ratios are for isolated material. Numbers in parentheses represent diastereomeric ratios observed in crude reaction mixtures. In some instances the minor diastereomer was partially or entirely removed during isolation.

[d] Isolated yield (average of two or more experiments).