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Palladium-Catalyzed Asymmetric Dearomatization of Naphthalene Derivatives

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The dearomatization of arenes is recognized as a chemical transformation of fundamental importance for organic chemists since it allows efficient access to the alicyclic frameworks present in many biologically active compounds.[1,2] In this context, complexation of the aromatic ring with stoichiometric amounts of transition metals,[3] the oxidation of phenols[4] and the reduction using metals in solution[5,6] have been widely investigated. Despite the importance of these methods, their requirement to use stoichiometric amounts of metals or reactive reagents and/or the additional complexation/decomplexation steps needed to release the desired product remains a limitation. Therefore, the development of new dearomatization methods that operate under catalytic conditions and with high stereocontrol would be extremely valuable for the synthetic organic community.[7] Herein, we present the first asymmetric transition-metal-catalyzed[8] dearomatization to form all-carbon quaternary stereocenter.[9]

Our initial idea is depicted in Scheme 1. As shown, the deprotonation of aniline **I** would be expected to increase the electron density in the adjacent aromatic ring, allowing the intramolecular electrophilic aromatic substitution-type reaction with the palladium (II) center to generate 3a*H*-indole derivative **III**.

To ascertain the feasibility of this hypothesis, we started our investigations with the transformation of **1a** into 6a-phenyl-6a*H*-benzo[a]carbazole **2a** using various Pd sources and phosphine ligands.[10] After some initial experimentation, we found that compound **2a** was produced in 98% yield when **1a** was treated with 3 mol% of $Pd(OAc)_2$, and 4.5 mol% of SPhos in dioxane at 80°C using LiO*t*-Bu as a base.[11]

With these results in hand, we next focused our efforts on the use of different chiral ligands to effect an asymmetric version of this transformation. The use of bidentate ligands resulted only in the recovery of starting material **1a** (Table 1, entries 1-2).[12] Better results were obtained, however, when monodentate ligands were used (Table 1, entries 4-6). Indeed, when MOP (**L4**) was employed, compound **2a** was obtained in 90% yield, albeit in only 21% ee. The enantioselectivity could be increased to 90% ee by using KenPhos[13] (**L5**) as a ligand (Table 1, entry 6). Further optimization of these conditions led to the formation of benzocarbazole **2a** in 96% yield and 93% ee when **1a** was treated with $Pd(dba)_2$ and KenPhos (**L5**) in THF (0.1 M) in presence of LiO*t*-Bu as a base (Table 1, entry13).

Encouraged by these initial findings, we next examined the scope of this transformation. First, we evaluated the effect of different substituents on the benzene ring. As shown in Table 2, both electron-donating (entry 2) and electron-withdrawing substituents (entries 3-4) formed the

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

corresponding benzocarbazole derivatives **2a-f** in good yields and enantioselectivities. Under these reaction conditions it was possible to obtain chlorine-substituted compound **2e** in 65% isolated yield and 89% ee. The efficacy of this method decreased, however, with the more sterically hindered *ortho*-substituted benzene derivatives. Thus, the reaction of *o*-Me substituted **1f** provided incomplete conversion to the corresponding benzocarbazole **2f** in 62% yield and 66% ee.

Following these experiments, we focused our attention on the substitution on the naphthalene ring. Our initial protocol using **L5** as a ligand provided the desired products in good yield even though in moderate enantioselectivity. After careful investigation we found that the use of bulkier ligand **L6**, in which one methyl group on the nitrogen had been replaced by an *i*-Pr residue, gave better results.[14] Indeed, when compounds **3a-d** were exposed to the standard conditions using **L6** in lieu of **L5**, benzocarbazoles **4a-d** were obtained in high yield and enantioselectivity (Table 3, entries 1-4). Again, the use of a more sterically hindered substrate resulted in a diminished ee (Table 3, entry 5). Compound **4c** proved to be crystalline, allowing the determination of the absolute configuration by means of X-Ray crystallographic analysis.[15]

The synthetic potential of these benzocarbazole derivatives is shown in Scheme 2. As depicted, the 1,2-addition of MeLi gave rise to the corresponding compound in 80% isolated yield as a 9:1 mixture of diastereomers (based on GC and GC-MS analysis of the crude reaction mixture) which were separated by column chromatography.[16] Protection of the secondary amine provided the crystalline compound **5** enantiomerically pure after crystallization.

In conclusion, we report the first asymmetric palladium-catalyzed intramolecular dearomatization reaction. The application of this new method to naphthalene derivatives led us to obtain benzocarbazole derivatives in high yields and enantioselectivities, making this method suitable for synthetic purposes. Further investigations into the mechanism of this reaction as well as extensions of the substrate scope are ongoing in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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(7). To the best of our knowledge, only two enantioselective oxidation of phenols have been describe: (a)Dohi T, Maruyama A, Takenaga N, Senami K, Minamitsuji Y, Fujioka H, Caemmerer SB, Kita

Y. Angew. Chem. Int. Ed 2008;47:3787.. (b)Vo NT, Pace RDM, O'Hara F, Gaunt MJ. J. Am. Chem. Soc 2008;130:404. [PubMed: 18081291].

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(9). For reviews on all-carbon quaternary stereocenters, see: (a)Corey EJ, Guzman-Perez A. Angew. Chem. Int. Ed 1998;37:388.. (b)Douglas CJ, Overman LE. Proc. Nat. Acad. Sci. USA 2004;101:5363. [PubMed: 14724294]. (c)Peterson EA, Overman LE. Proc. Nat. Acad. Sci. USA 2004;101:11943. [PubMed: 15232003]. (d)Trost BM, Jiang C. Synthesis 2006:0369..

(10). For a photochemical synthesis of 6-Methyl-6a*H*-benzo[a]carbazoles and relative compounds, see: (a)Kulagowski JJ, Mitchell G, Moody CJ, Rees CW. J. Chem. Soc., Chem. Commun 1985:650.. (b)Kulagowski JJ, Moody CJ, Rees CW. J. Chem. Soc., Perkin. Trans 1985;1:2733..

(11). LiHMDS, NaO*t*-Bu, and NaHMDS also promoted this transformation albeit with lower yields. Notably, no reaction occurred when the potassium bases were used. At present, we have no explanation for the lack of reactivity with potassium bases.

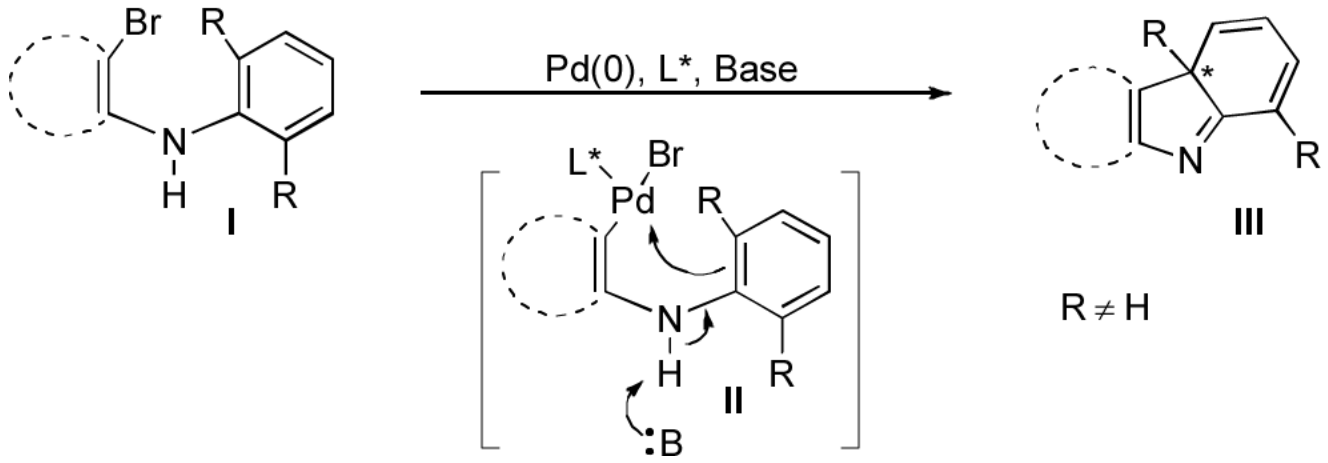
(12). The use of TangPhos as a ligand led to a 26% yield of **2a**, presumably due to monodentate behavior of this ligand under the reaction conditions.

(13). Chieffi A, Kamikawa K, Åhman J, Fox JM, Buchwald SL. Org. Lett 2001;3:1897. [PubMed: 11405739]

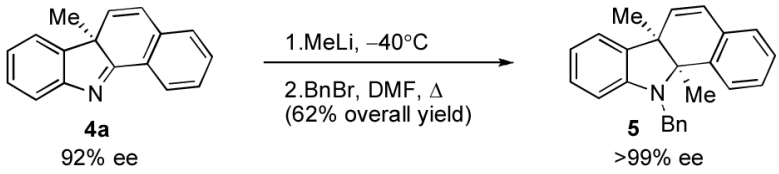
(14). The improvements on the ee were up to 16% in some cases. Interestingly, when ligand **L6** was used for compounds **1a-f** no improvement or even a slight erosion in the ee was found.

(15). The crystalline sample was obtained using (*S*)-KenPhos.

(16). The absolute configuration of the major diastereomer was determined by single crystal X-Ray diffraction. (see supporting information).



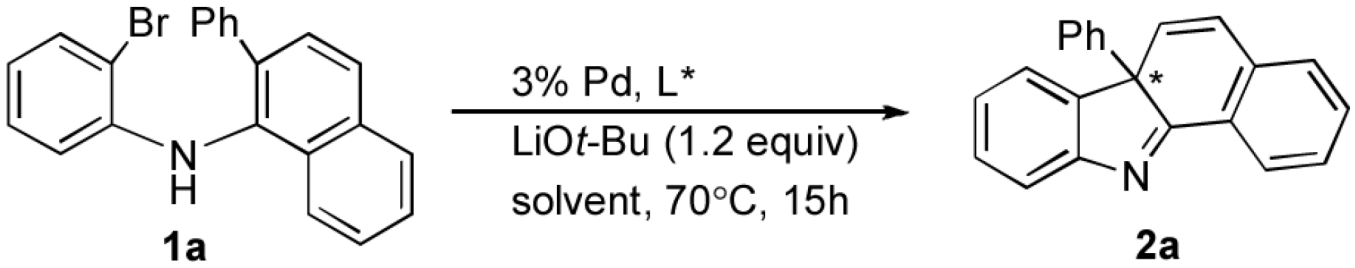
Scheme 1.
General scheme for the Pd-catalyzed dearomatization.



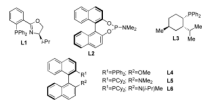
Scheme 2.
Further functionalization of derivative **4a**

Table 1

Screening of dearomatization conditions.[a]



entry	L*	Pd	Pd:L	solvent	yield(%)[b]	ee(%)[c]
1	(*S*)-BINAP	$Pd(OAc)_2$	1:2	Dioxane	0	-
2	**L1**	$Pd(OAc)_2$	1:2	Dioxane	0	-
3	**L2**	$Pd(OAc)_2$	1:2	Dioxane	0	-
4	**L3**	$Pd(OAc)_2$	1:2	Dioxane	90	16 (*S*)
5	**L4**	$Pd(OAc)_2$	1:2	Dioxane	89	21 (*S*)
6	**L5**	$Pd(OAc)_2$	1:2	Dioxane	80	90 (*S*)
7	**L5**	$Pd(OAc)_2$	1:2	Toluene	21	89 (*S*)
8	**L5**	$Pd(OAc)_2$	1:2	DMF	69	60 (*S*)
9	**L5**	$Pd(OAc)_2$	1:2	THF	84	93 (*S*)
10	**L5**	$Pd(dba)_2$	1:2	THF	96	93 (S)
11	**L5**	$[allylPdCl]_2$	1:2	THF	87	93 (*S*)
12	**L5**	$Pd(dba)_2$	1:1	THF	81	93 (*S*)
13	**L5**	$Pd(dba)_2$	1:1.5	THF	96	93 (*S*)



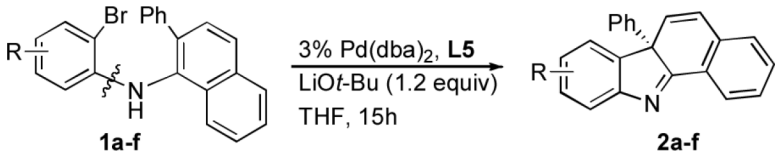
[a]Reaction conditions: Aniline (0.1 mmol) in solvent (1 mL).

[b]GC yields using dodecane as an internal standard.

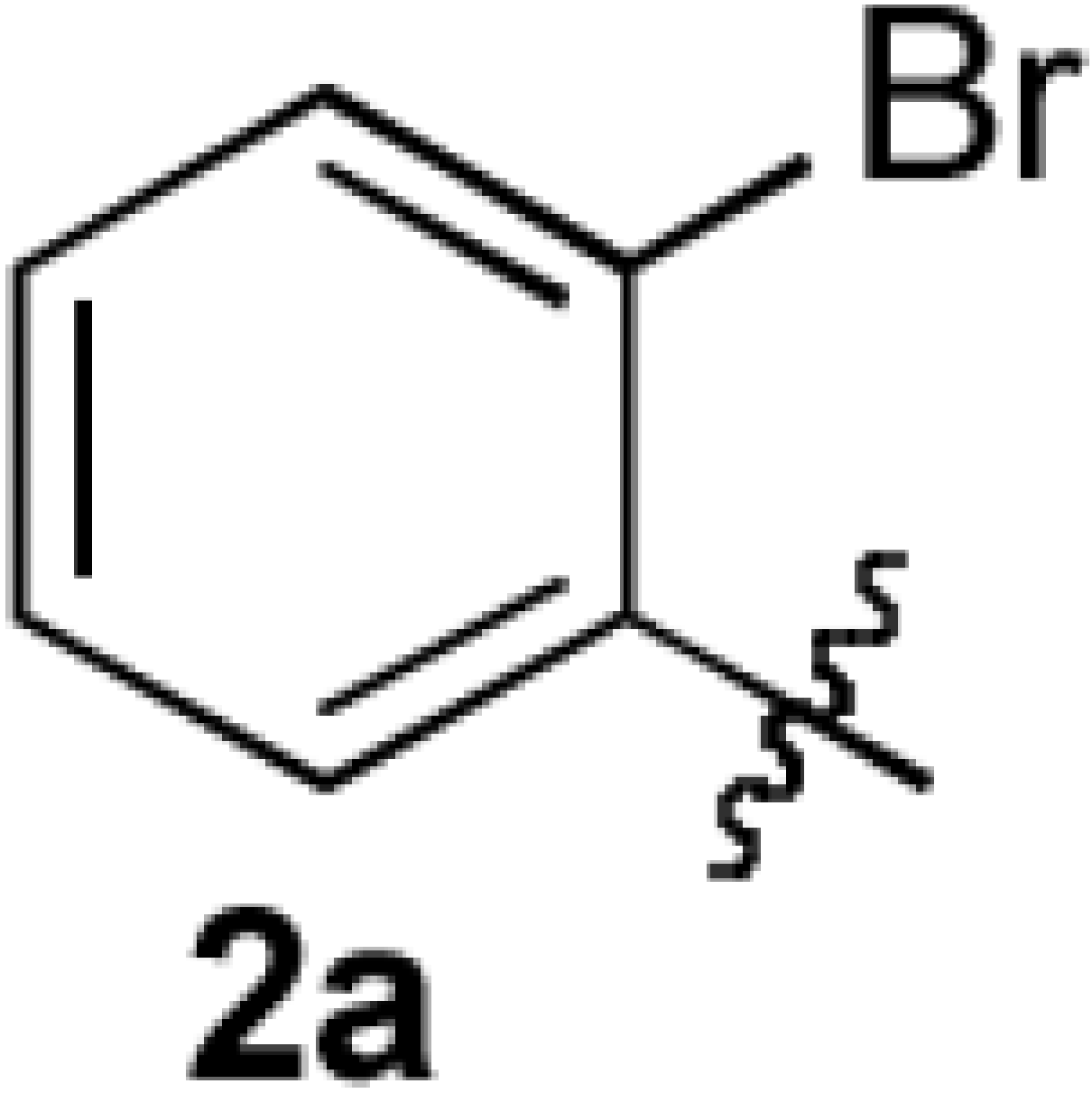
[c]The ee values were determined by HPLC (see supporting information). The absolute configuration was determined by single crystal X-Ray diffraction (see text and supporting information).

Table 2

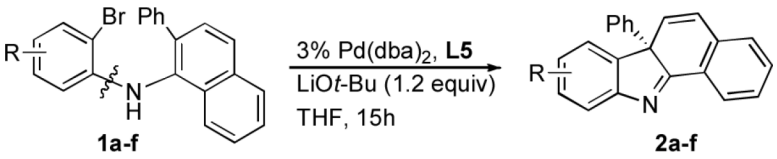
Influence of the substitution on the benzene nng.[a]

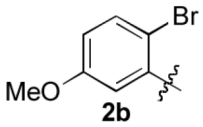
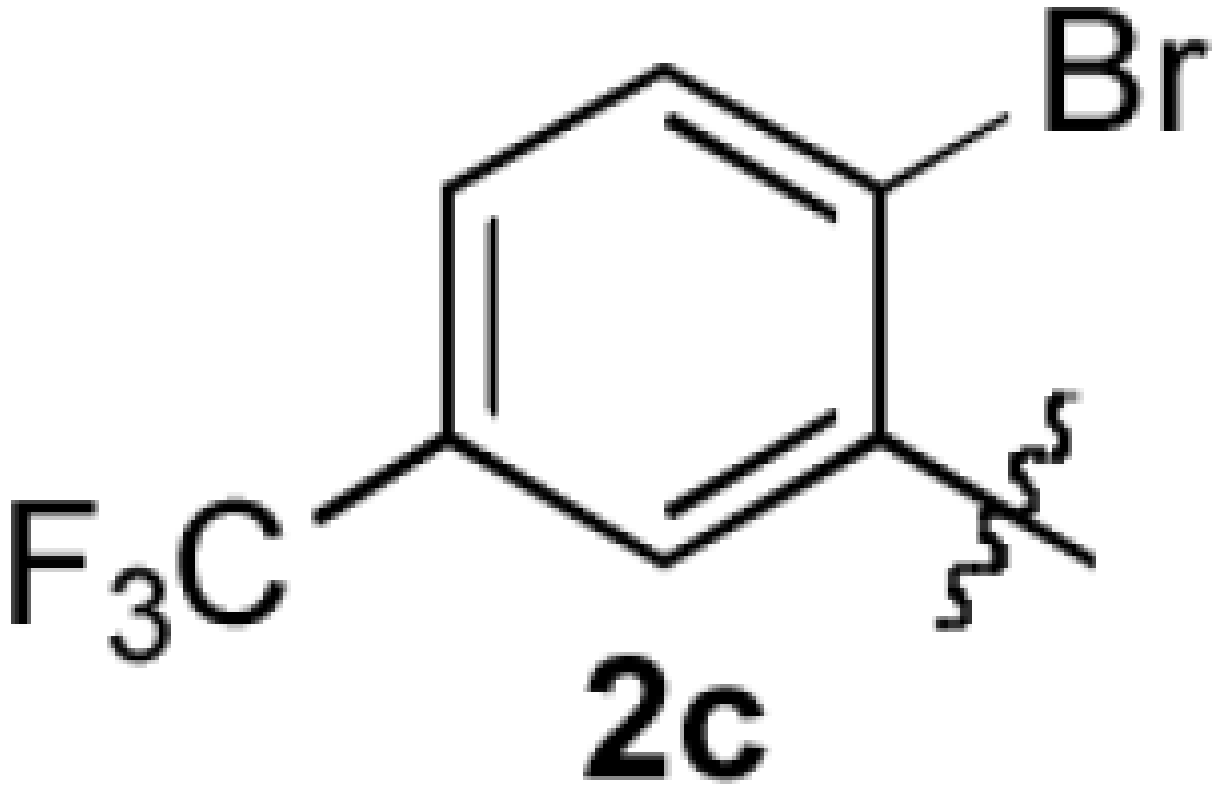


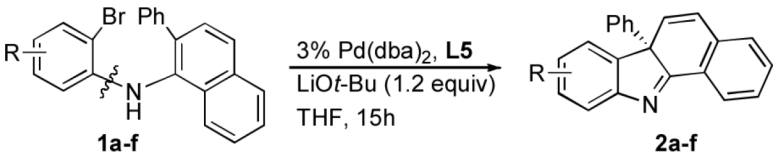
1a-f 2a-f

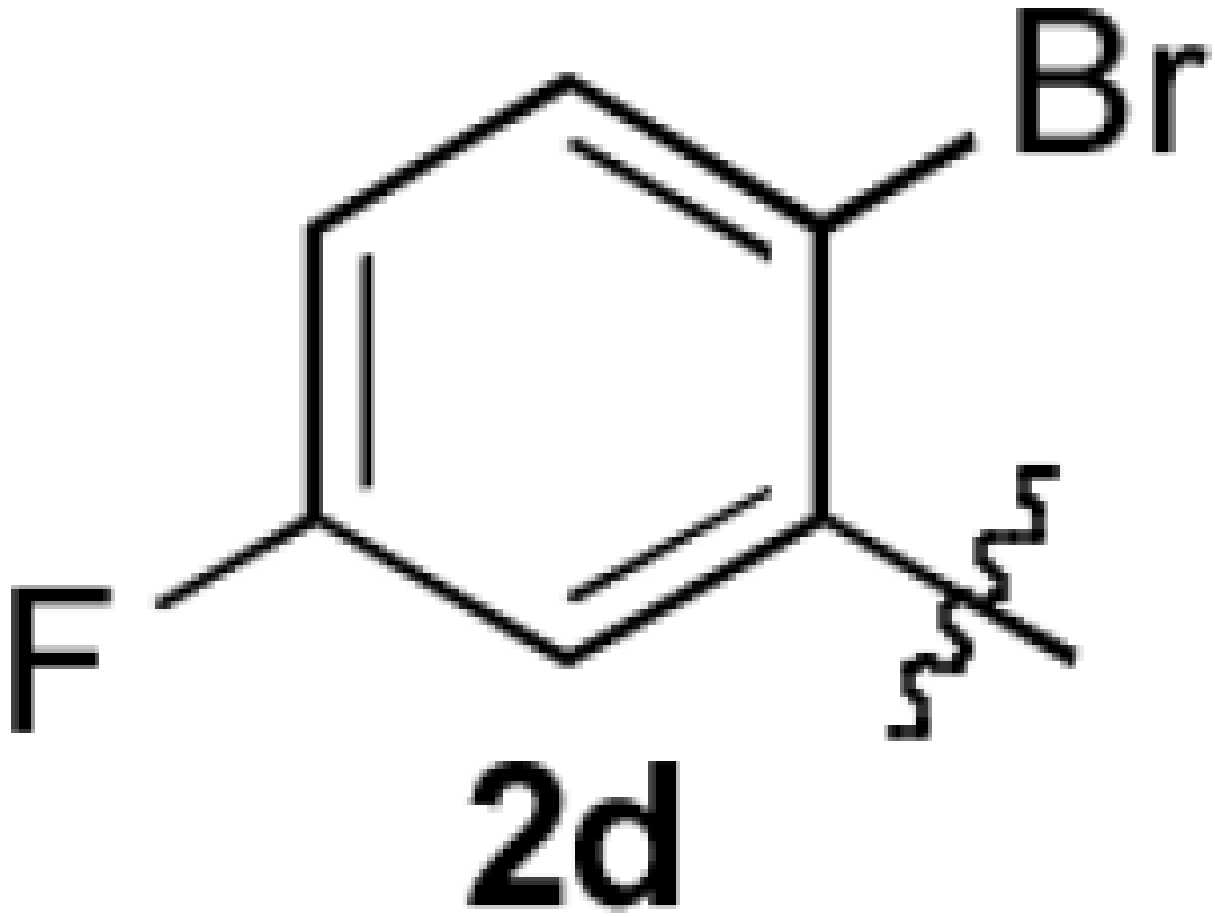
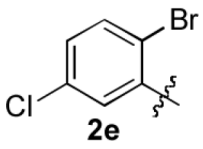
entry	Ar	T(°C
1		70

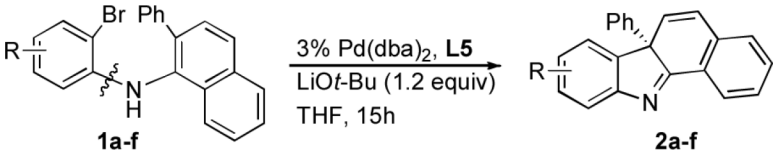
2a

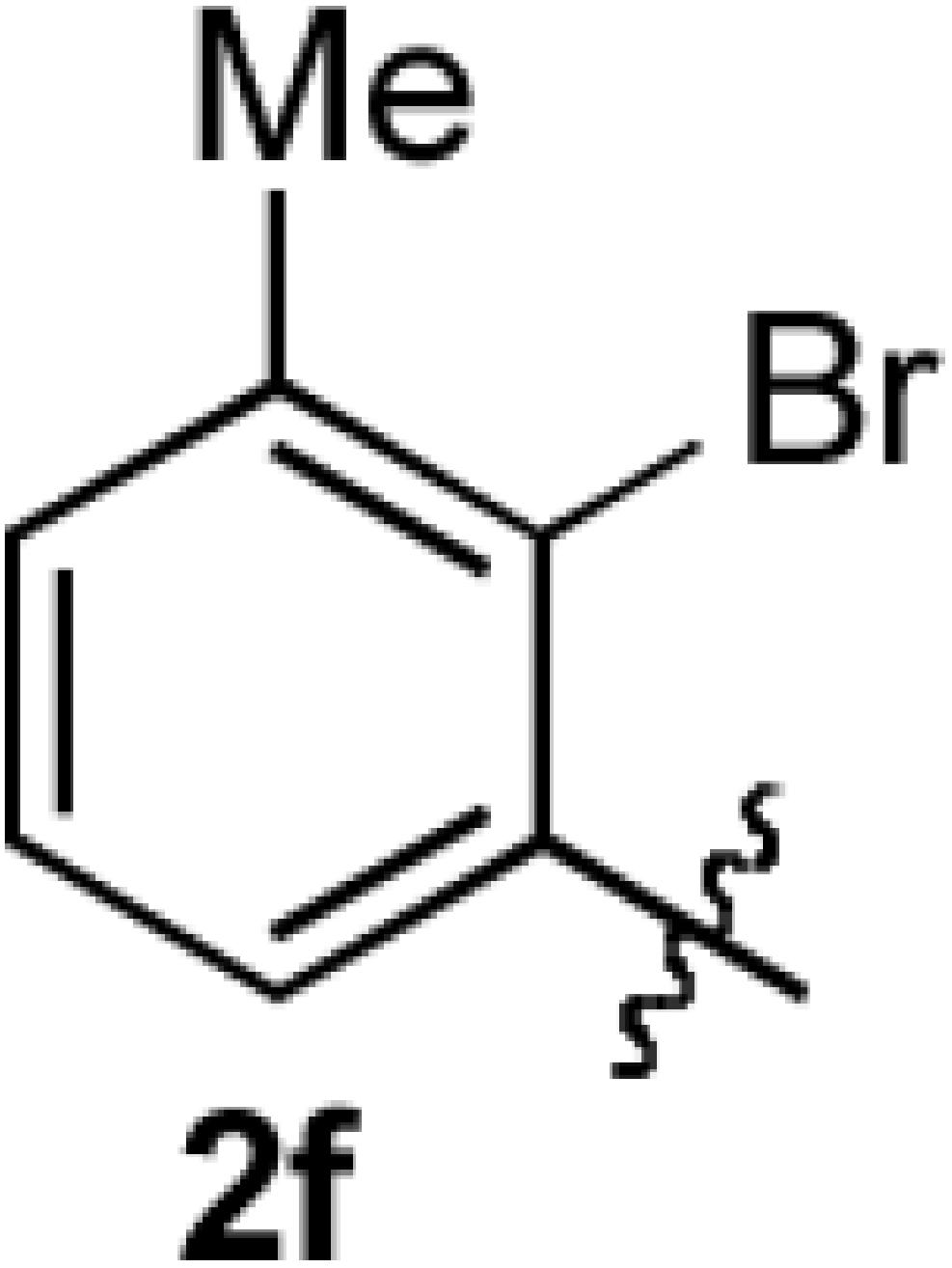


entry	Ar	T(°C
2	 2b	100
3	 2c	70



entry	Ar	T(°C
4	 2d	80
5	 2e	70



entry	Ar	T(°C
6		100

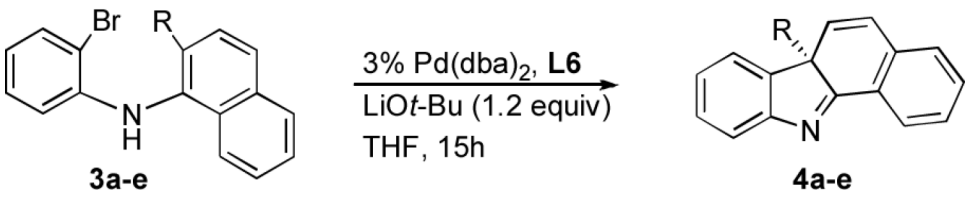
[a] Reaction conditions: Aniline (0.5 mmol), $Pd(dba)_2$ (3 mol%), L5 (4.5 mol%) in THF (5 mL).

[b] Isolated yields are an average of two runs. The ee values were determined by HPLC (see supporting information).

[c] Incomplete conversion of the starting material.

Table 3

Influence of naphthalene substitution.[a]



entry	R	T(°O	yield(%)[b]	ee(%)[c]
1	Me (**3a**)	90	83	92 (*R*)
2	*n*-Pr(**3b**)	90	79	88 (*R*)
3	4-ClC_6H_4 (**3c**)	70	89	93 (*S*)
4	2-(MeO)C_6H_4 (**3d**)	90	93	90 (*R*)
5	2-MeC_6H_4 (**3e**)	100	64[d]	50 (*S*)

[a] Reaction conditions: Aniline (0.5 mmol), $Pd(dba)_2$ (3 mol%), L6 (4.5 mol%) in THF (5 mL).

[b] Isolated yields are an average of two runs.

[c] The ee values were determined by HPLC (see supporting information).

[d] Incomplete conversion of the starting material.