Unleashing the Power of Alkali-Metal Mediation for Arene Functionalisation and Catalysis



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Ischia Advanced School of Organic Chemistry

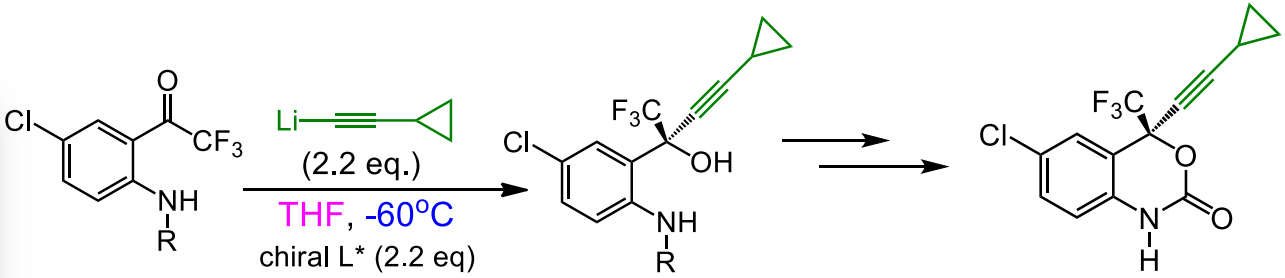
19th September 2026

UNIVERSITÄT BERN

Organolithium Reagents, the Workhorses of Synthesis



W. Schlenk,
Ber. Dtsch. Chem. Ges.
1917, *50*, 262

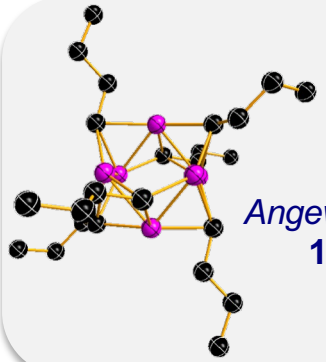


Efavirenz (Antiretroviral)

(€3.11 billion per year)

- ✓ vast uses in synthesis
- ✓ commercially available
- ✓ high reactivity
- ✓ soluble in hydrocarbon solvents





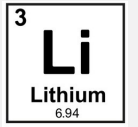
$[^{n}BuLi]_6$

D. Stalke,
Angew. Chem, Int. Ed.
1993, *32*, 580

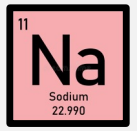
Heavier Alkali-Metal Reagents (NaR, KR)



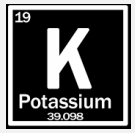
J. A. Wanklyn,
Proc. R. Soc.
1858, *9*, 341



Abundance: 0.002 %
Electronegativity: 0.98
Size: 145 pm



Abundance: 2.6 %
Electronegativity: 0.93
Size: 180 pm



Abundance: 2.4 %
Electronegativity: 0.82
Size: 235 pm

Main Limitations of NaR, KR

- **Lack of solubility**
- **Too reactive**
- **Lack of thermal stability**
- **non-commercially available**

Renaissance of MR (M = Na, K) in Organic Chemistry

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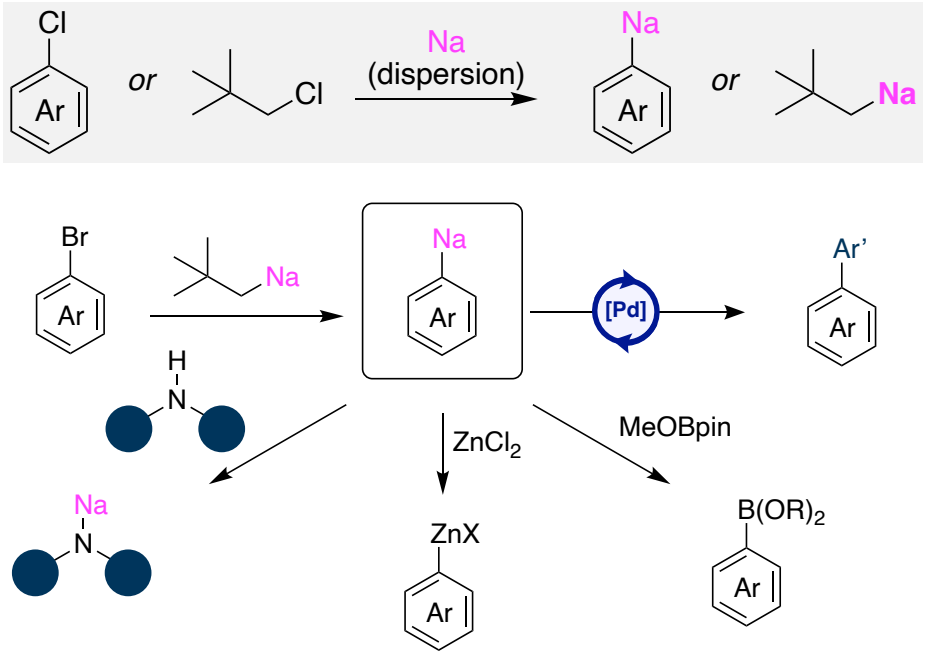
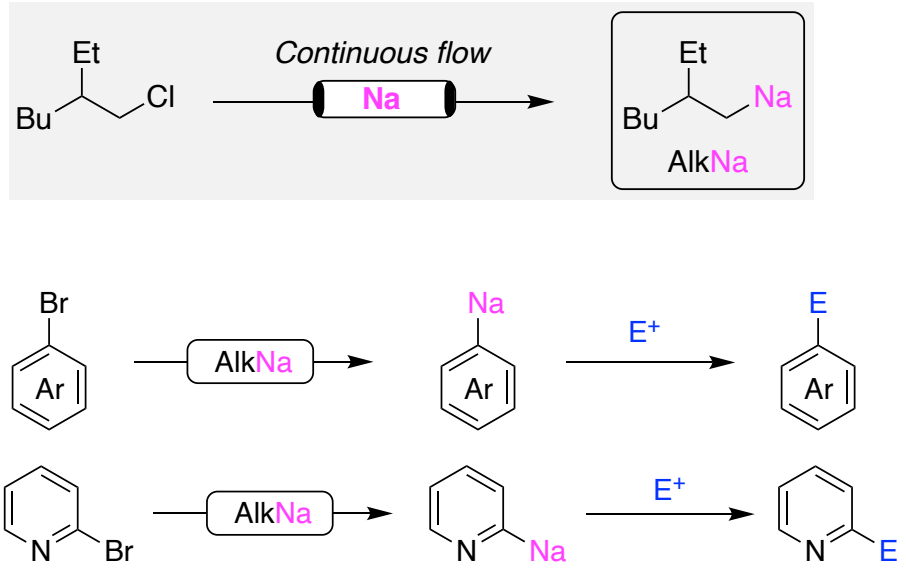
Na dispersion



S. Asako, K. Takai, L. Ilies, *Nat.Cat.* **2019**, *2*, 297;
Adv. Synth. Cat. **2019**, *361*, 3120; *Commun. Chem.* **2021**, *4*, 76

Na-packed bed reactor

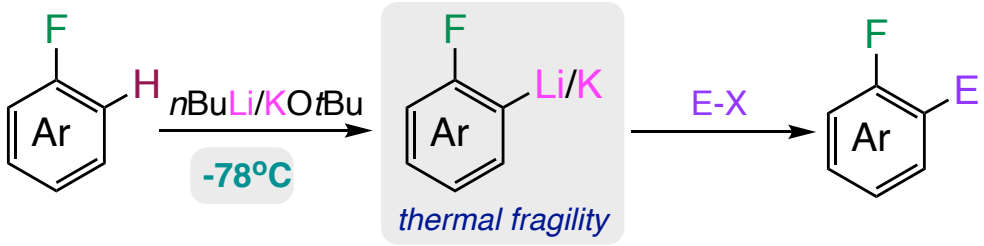


P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14296;
Angew. Chem. Int. Ed. **2022,** *61,* e202203807

NaAr intermediates are prepared *in situ*!

Potassium Mediated Zincation Reactions

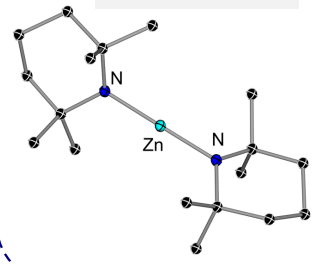
Metalation of fluoroarenes



Lochmann-Schlosser "LICKOR" Superbase

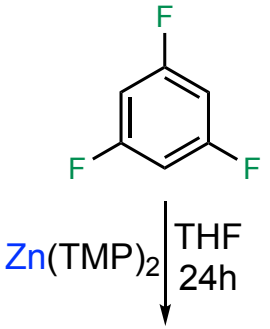
M. Schlosser, *Tetrahedron Lett.* **1996**, *36*, 6551

$Zn(TMP)_2$

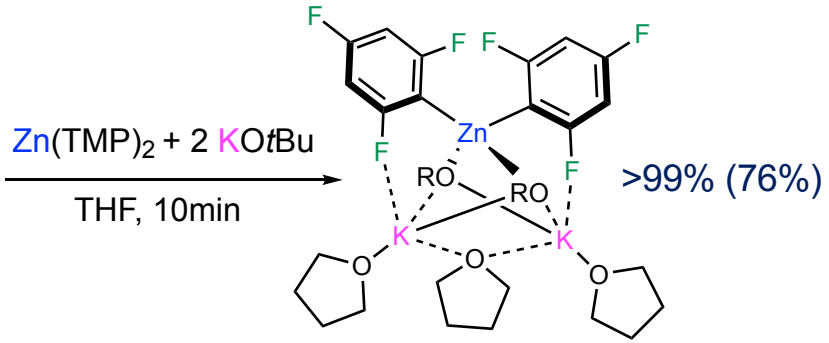




0.5M solution
in toluene



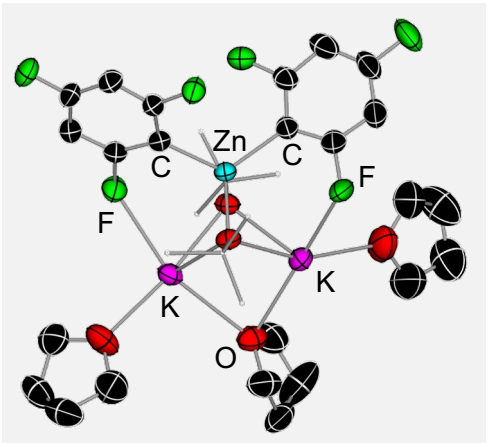
no reaction



>99% (76%)



Neil Judge

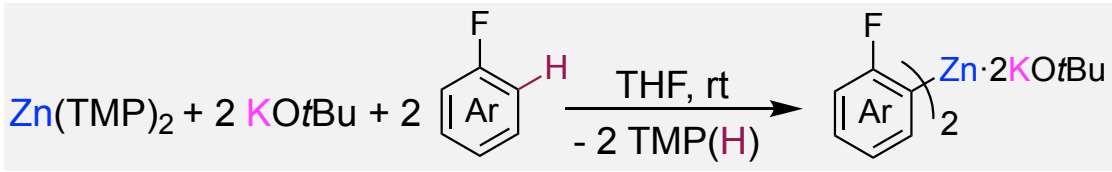


thermally stable intermediate
Zn-C vs K-F bonding
higer order zincate (2:1 K:Zn)

direct Zn-H exchange
two fold activation of
$Zn(TMP)_2$!

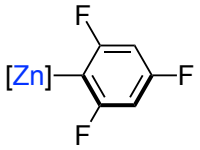
Angew. Chem. Int. Ed. **2023**, *63*, e202303099

Potassium Mediated Zincation of Fluoroarenes

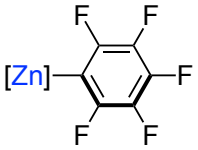


Yields determined by ^{1}H NMR spectroscopy, isolated yields shown in brackets

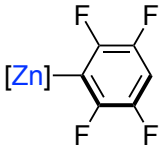
polyfluorinated aromatics



10 min, >95%
(76%)

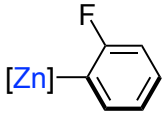


10 min, >95%
(70%)

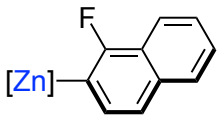


10 min, >95%
(64%)

non-activated fluoroarenes

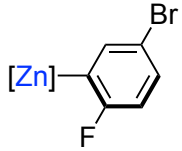


24 h, >95%
(65%)

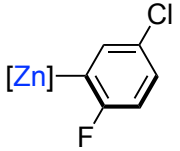


24 h, 82%
(75%)

p-substituted halofluoroarenes

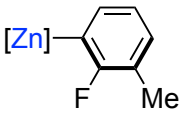


1 h, >95%
(72%)

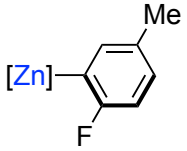


1 h, >95%
(73%)

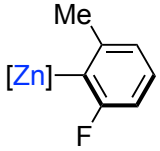
fluorotoluenes



24 h, >95%
(85%)

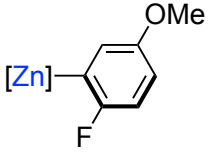


24 h, >95%
(81%)

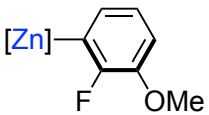


24 h, >95%
(70%)

fluoroanisoles

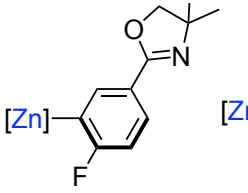


24 h, >95%
(57%)

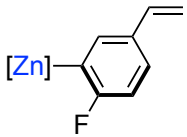


24 h, 90%
(67%)

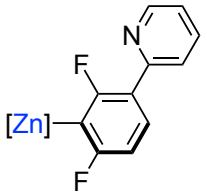
miscellaneous fluoroarenes



24 h, 93%
(76%)



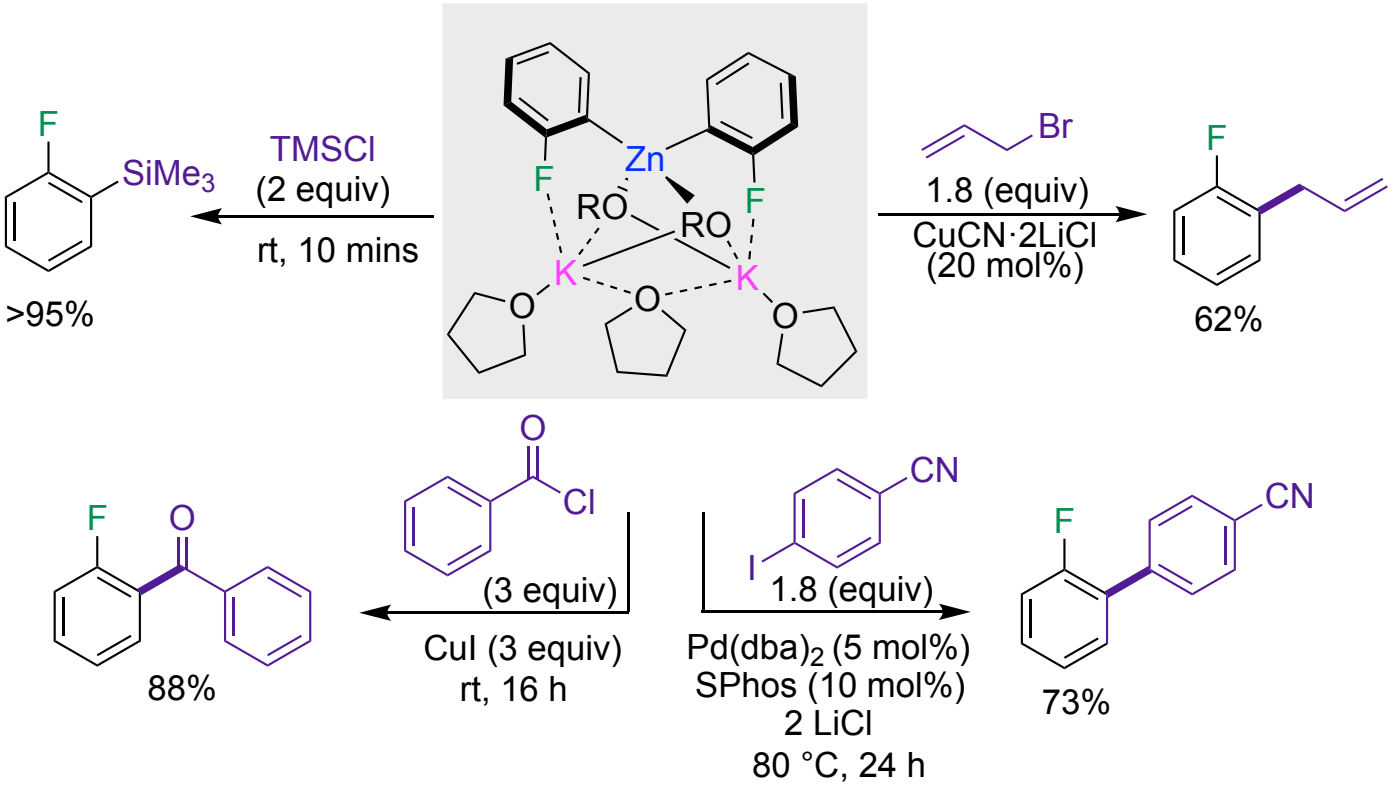
3 h, >95%
(67%)



10 min, >95%
(78%)

Angew. Chem. Int. Ed. **2023**, *63*, e202303099

Potassium Mediated Zincation of Fluoroarenes



Angew. Chem. Int. Ed. **2023**, *63,* e202303099

Potassium Mediated Zincation of Non-activated Substrates

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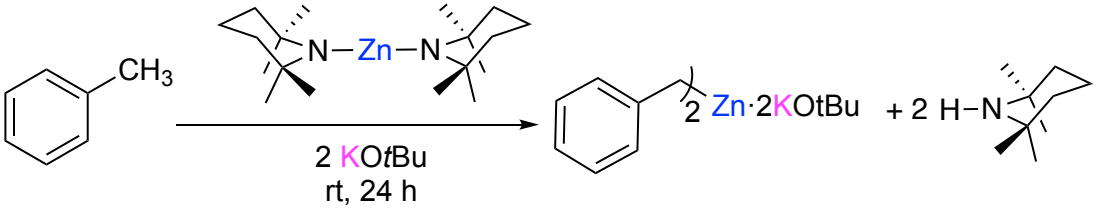
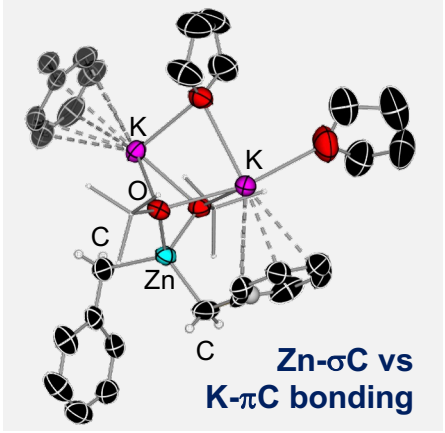
$Zn(TMP)_2$

commercially available
0.5M solution in toluene

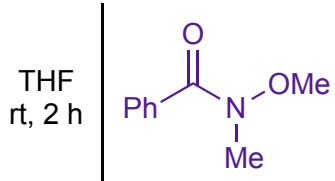


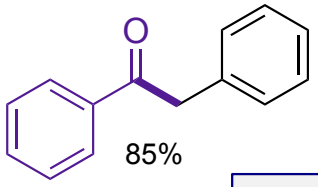


30 min, 95% 30 min, 89%



Zn-σC vs K-πC bonding



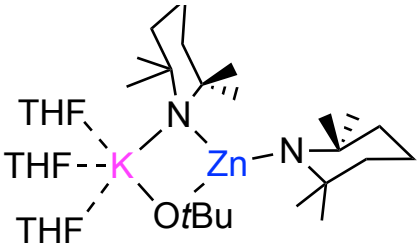


drastic alkali-metal effect:
✗ Li, Na ✓ K

Benzylic aroylation of toluene

zincate modification:
enhanced basicity and Nu power

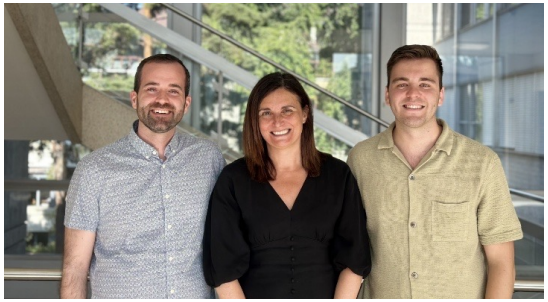
mechanistic studies



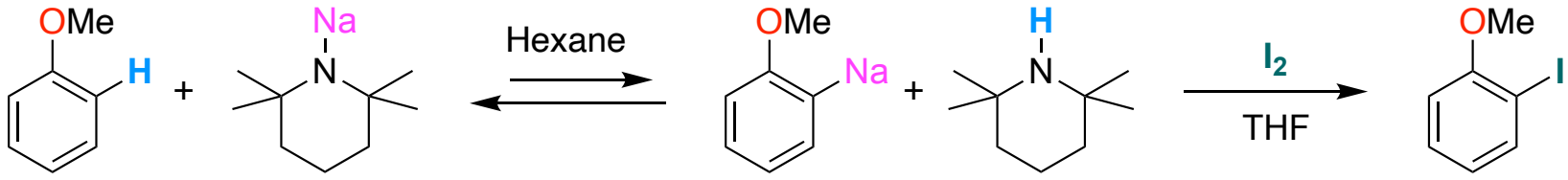
active base:
potassium zincate

Chem. Sci. **2024**, *15*, 14757

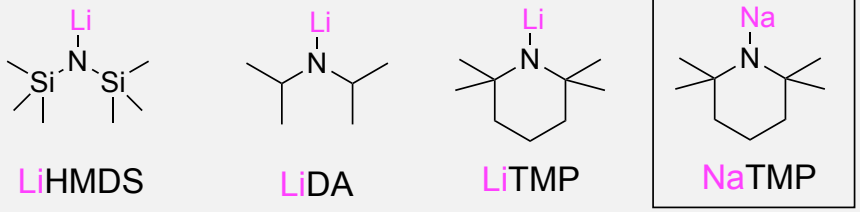
For a Tutorial Review on this topic:
Chem. Soc. Rev. **2026**, *55*, 8382

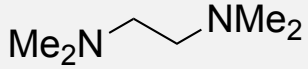


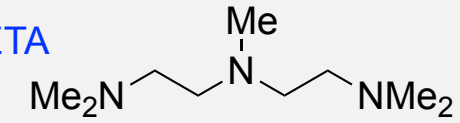
Assessing Directed-*ortho*-Sodiation of Anisole

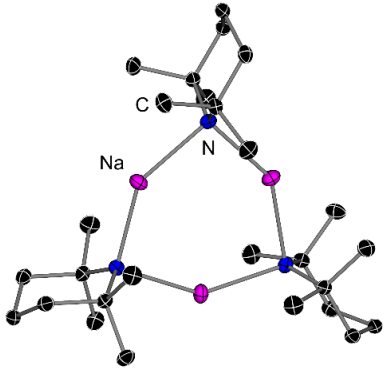


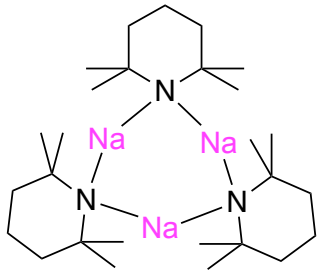
Traditional non-nucleophilic strong bases:



TMEDA  34%

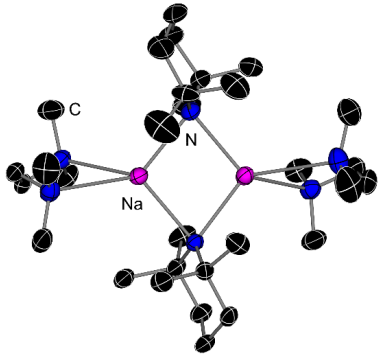
PMDETA  36%

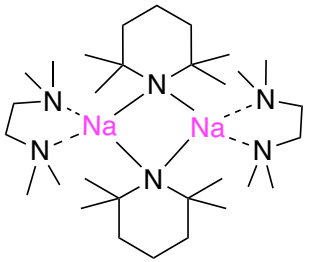




[NaTMP]$_3$

M. F. Lappert, R. E. Mulvey
J. Organomet. Chem., **1999**, *587*, 88





[NaTMP·TMEDA]$_2$

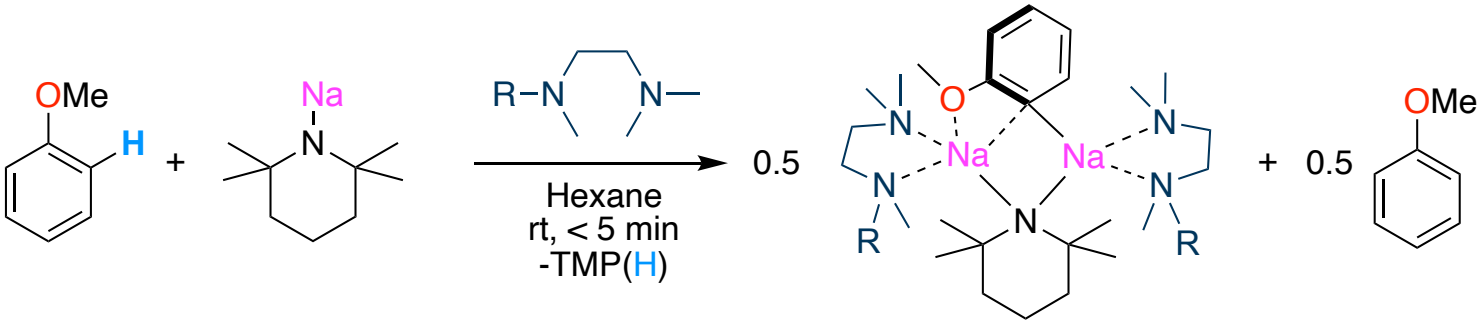
C. T. O'Hara,
Chem. Eur. J., **2008**, *14*, 8025

dimeric structure retained in solution

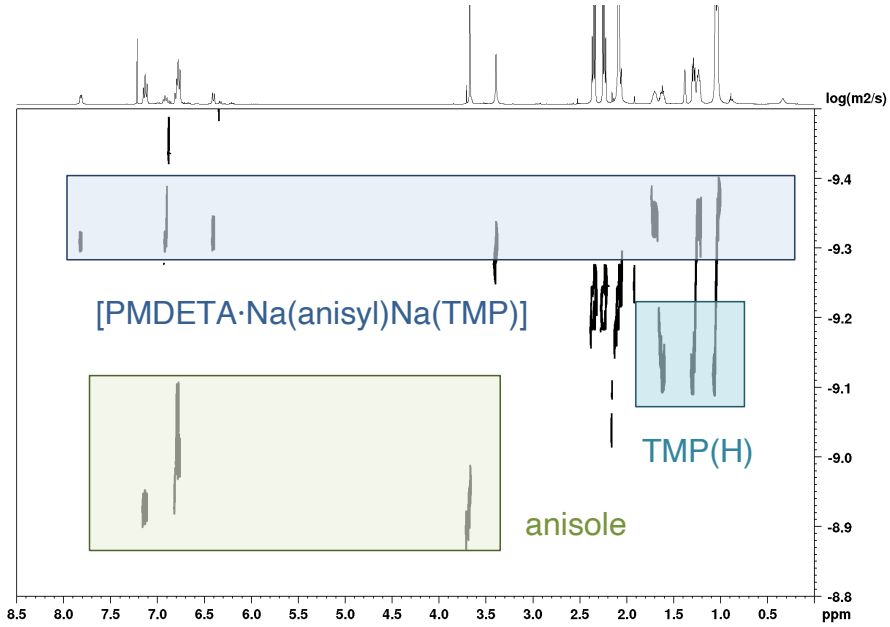


Andreu Tortajada

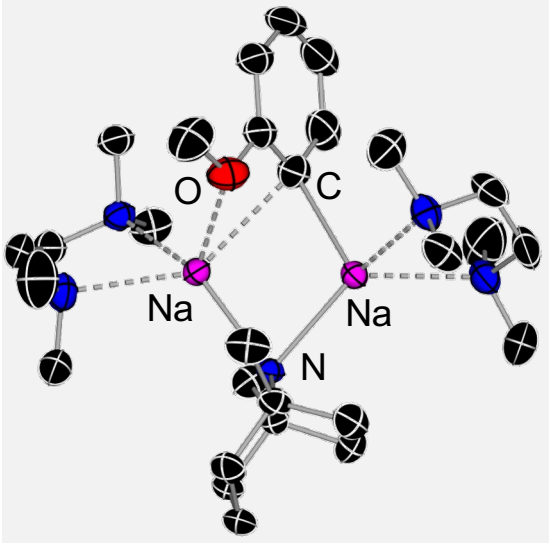
Assessing Directed-*ortho*-Sodiation of Anisole



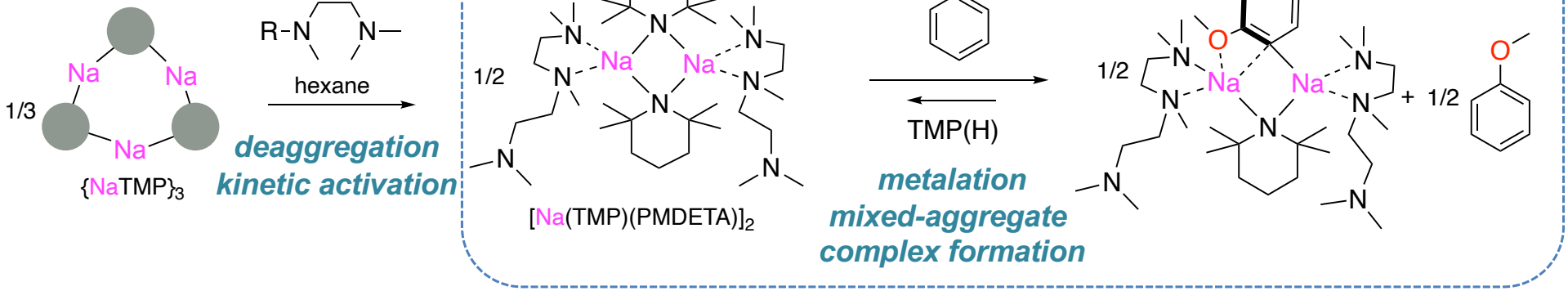
- mixed-aggregate intermediate
- structure retained C_6D_{12} solution
- **43%** metalation

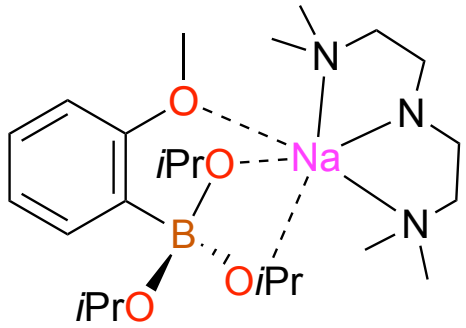


^{1}H-DOSY NMR, C_6D_{12}, 300.1 MHz, 298 K



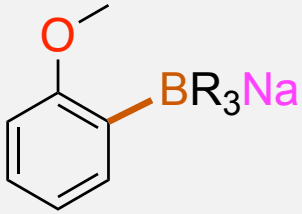
Sodium Mediated Borylation Approaches





BX_3 — *aryl trapping equilibrium shift*

$B(OiPr)_3$ 83% yield



$B(OMe)_3$ 10% yield

$B(OMe)_3$ reacts with [NaTMP·PMDETA]$_2$

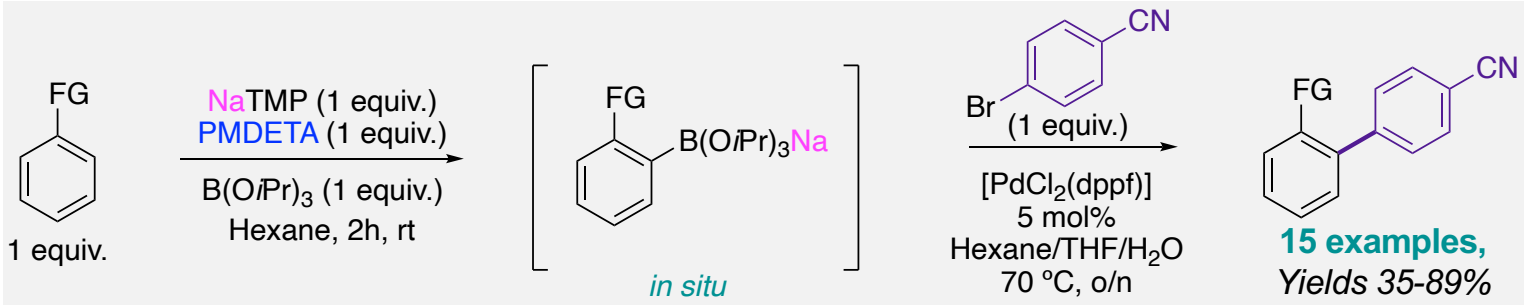
base degradation

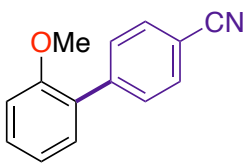
steric incompatibility of $B(OiPr)_3$ with [NaTMP·PMDETA]$_2$

LiTMP, 13% KTMP, 5%

Angew. Chem. Int. Ed. **2022**, *61*, e202204262
Chem. Sci. **2023**, *14*, 6538

Applications in Suzuki-Miyaura Couplings





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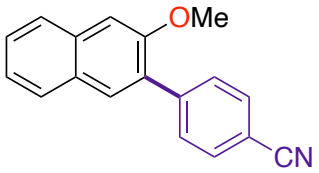

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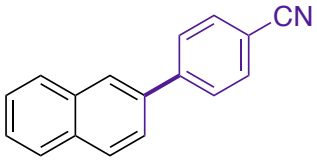
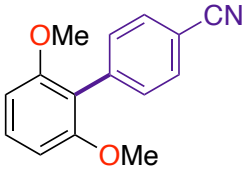


76%



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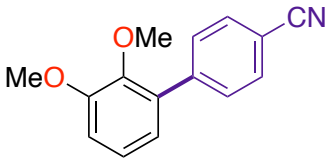
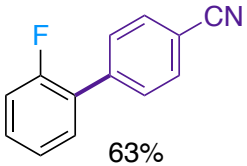
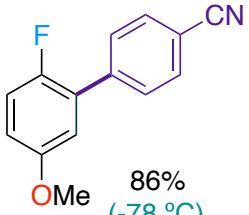


64%



63%
(-78 ºC)



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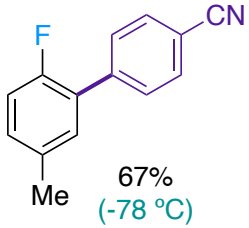

67%
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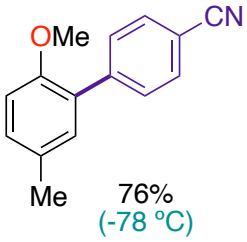

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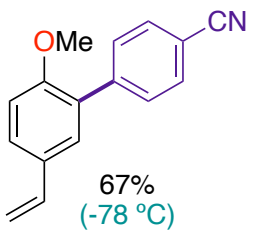
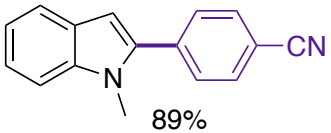


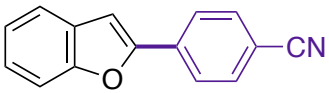
67%
(-78 ºC)



89%



71%



83%

Limitations

- ✗ Cl, Br, CO_2R substituents
- ✗ low T (-78ºC) for ArF
- ✗ unsuccessful for diborylations
- ✗ no compatible with pyridines

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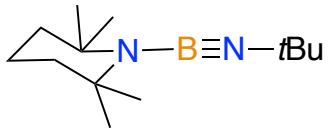
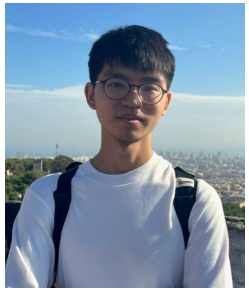
Using an Amino(imino)borane as a Trapping Agent



amino(imino)borane

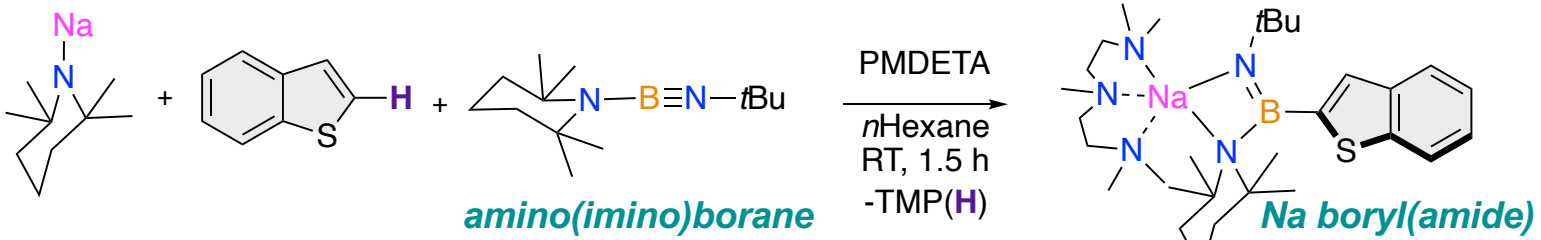
H. Nöth, *Eur. J. Inorg. Chem.* **2004**, 3612

sp-hybridised B: highly electrophilic
bulky substituents: precude oligomerisation



Clarence Tan

Using an Amino(imino)borane as a Trapping Agent

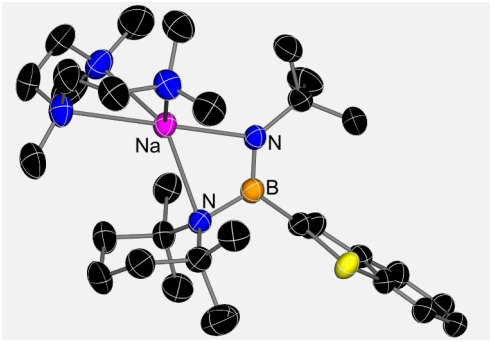


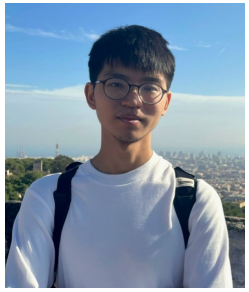
amino(imino)borane

Na boryl(amide)

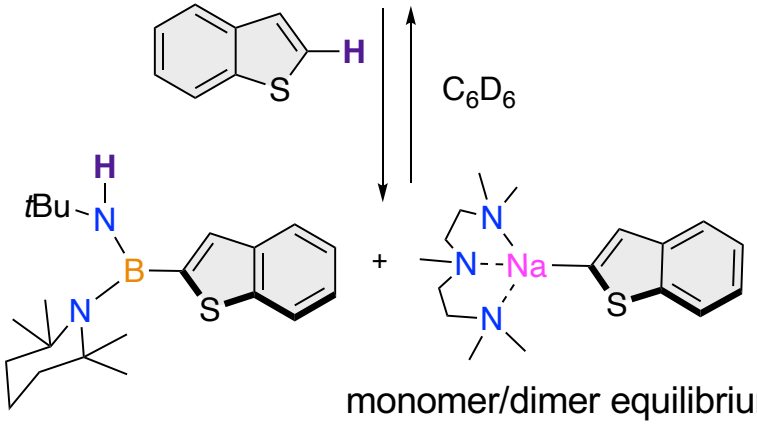
95% yield

H. Nöth, *Eur. J. Inorg. Chem.* **2004**, 3612



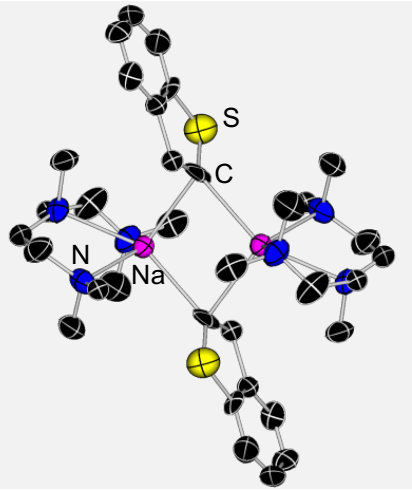


Clarence Tan

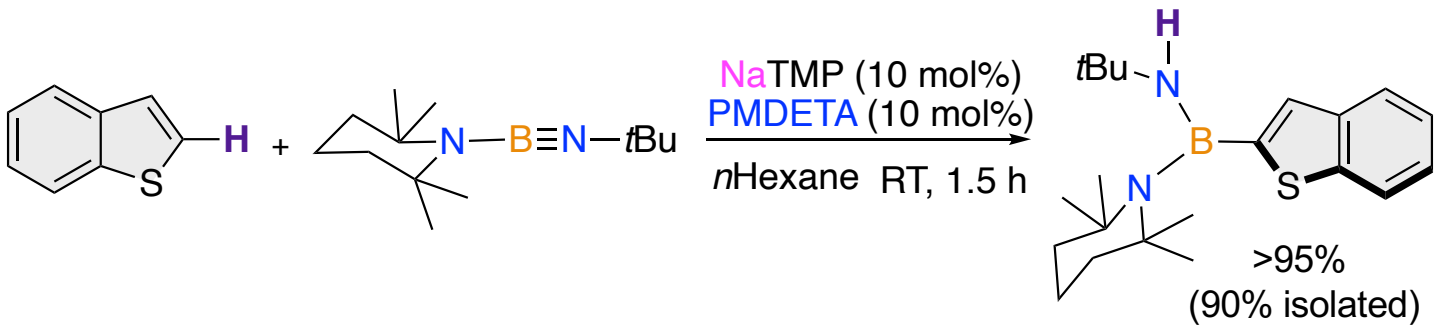


monomer/dimer equilibrium in C_6D_6 solution

(^{1}H DOSY NMR)

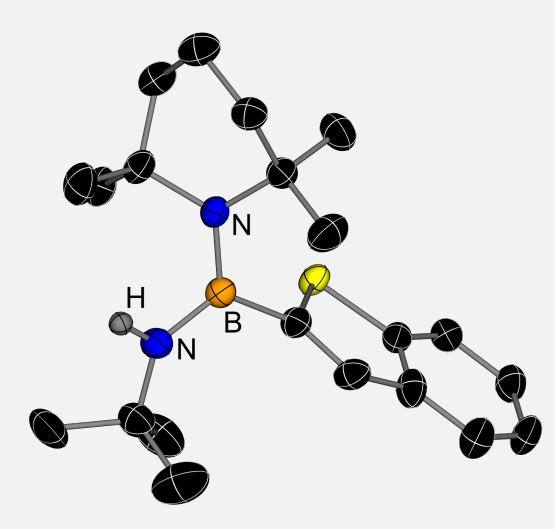


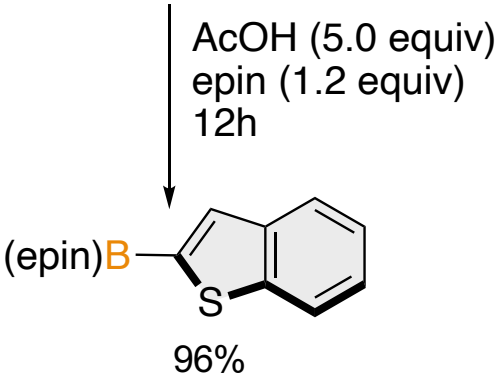
Upgrading Deprotonative Borylation to Catalytic Regimes

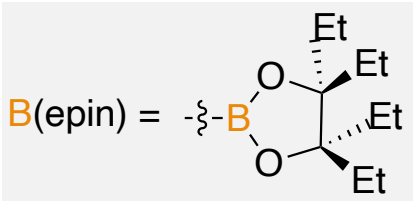


Sodium-Catalysed Deprotonative Borylation!

LiTMP, 6%
NaHMDS, 34%

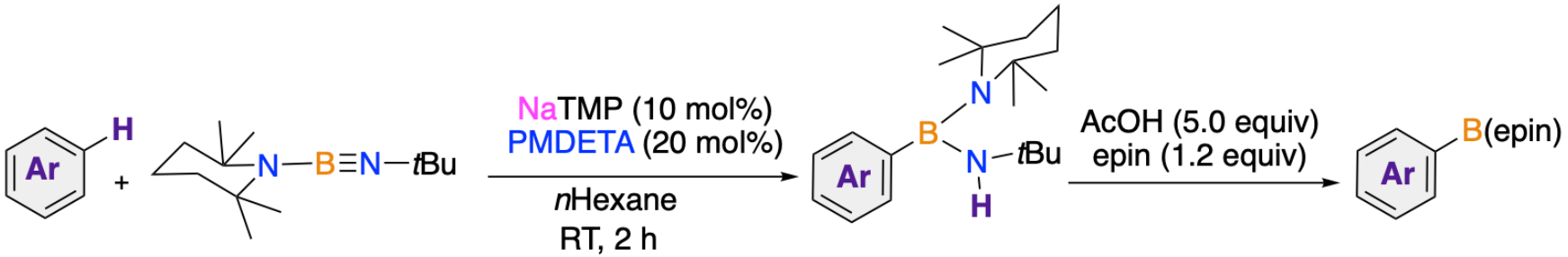


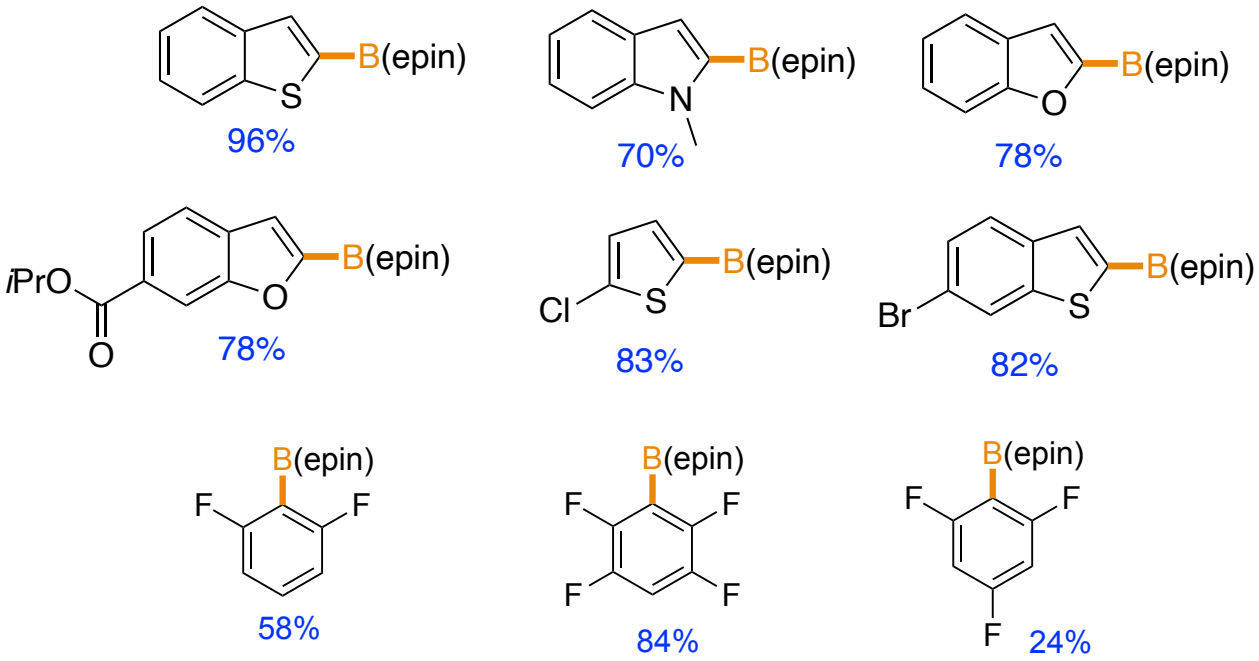




J. Am. Chem. Soc.,**2025**, *147*, 42076

Upgrading Deprotonative Borylation to Catalytic Regimes





Key advantages

- ✓ Compatible with Cl, Br substituents
- ✓ Controlled di-borylation
- ✓ Room temperature borylation ArF
- ✓ Remarkable stoichiometric control

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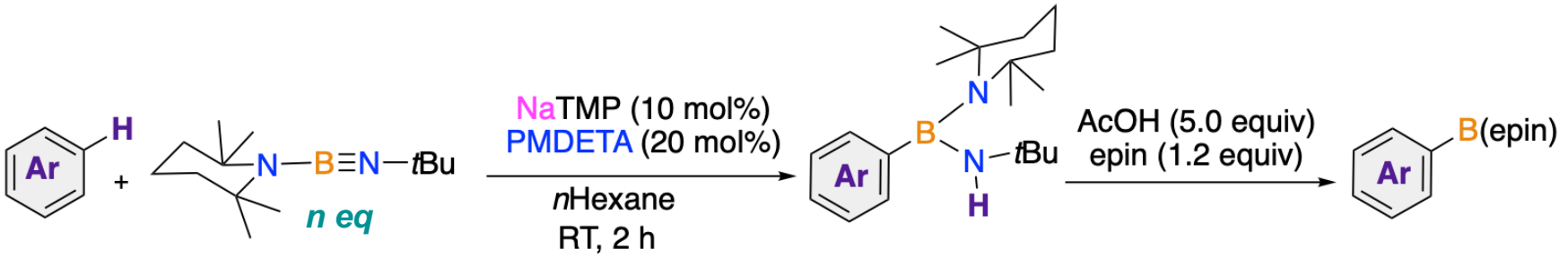
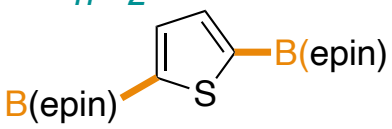
Upgrading Deprotonative Borylation to Catalytic Regimes

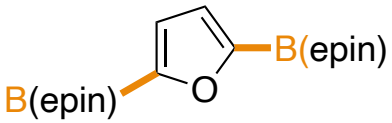


Iterative Borylations

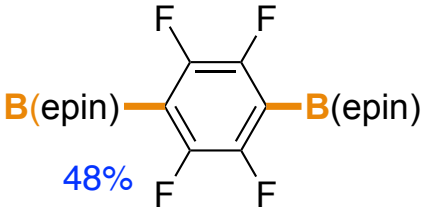
n =2



88%

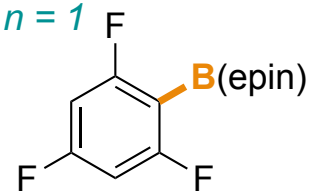


94%



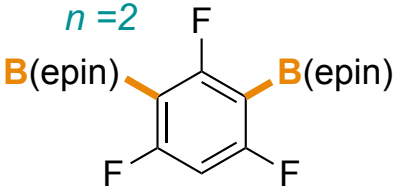
48%

n = 1



24%

n =2



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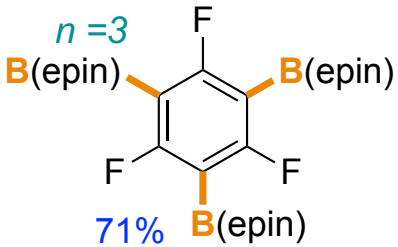
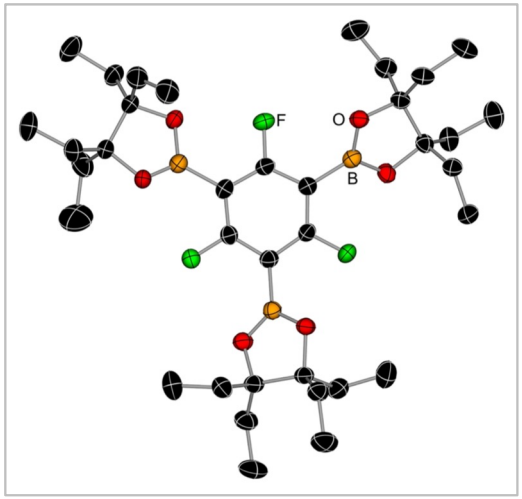
n =3



71%



excellent stoichiometric control

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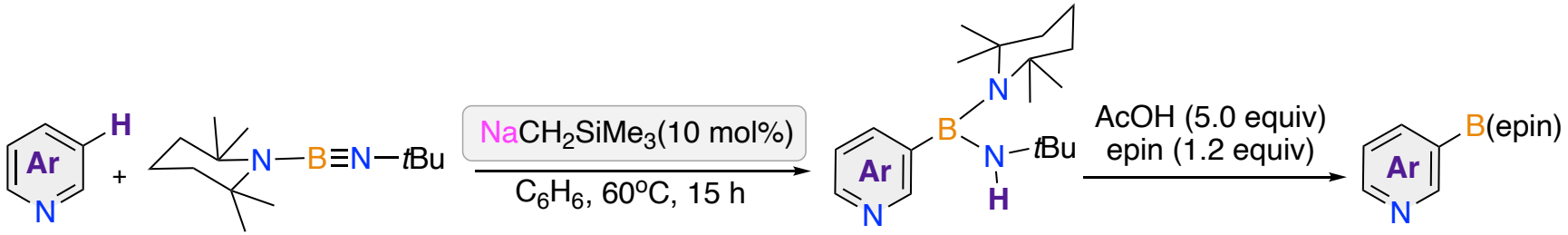
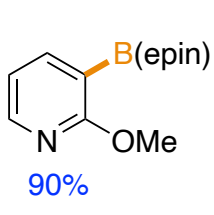
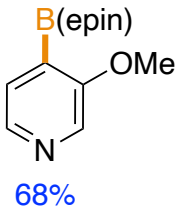
Upgrading Deprotonative Borylation to Catalytic Regimes

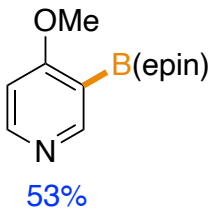




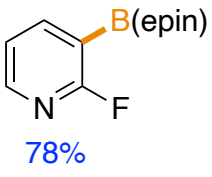
90%



68%



53%



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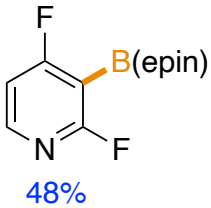

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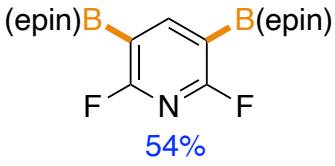

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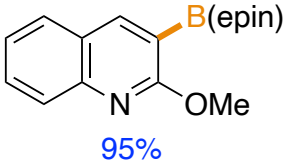

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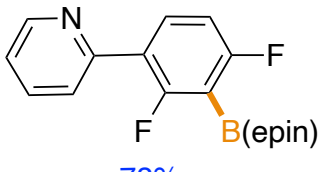
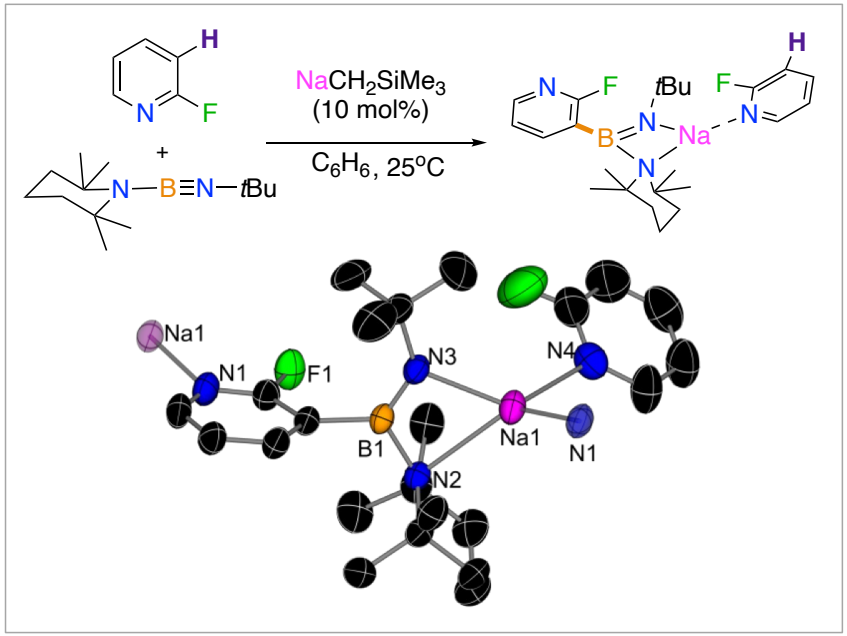


78%

Catalytic deprotonative borylation of pyridines



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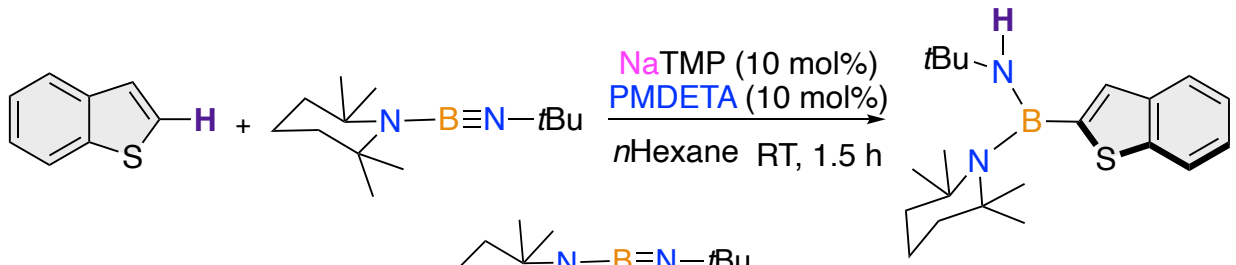
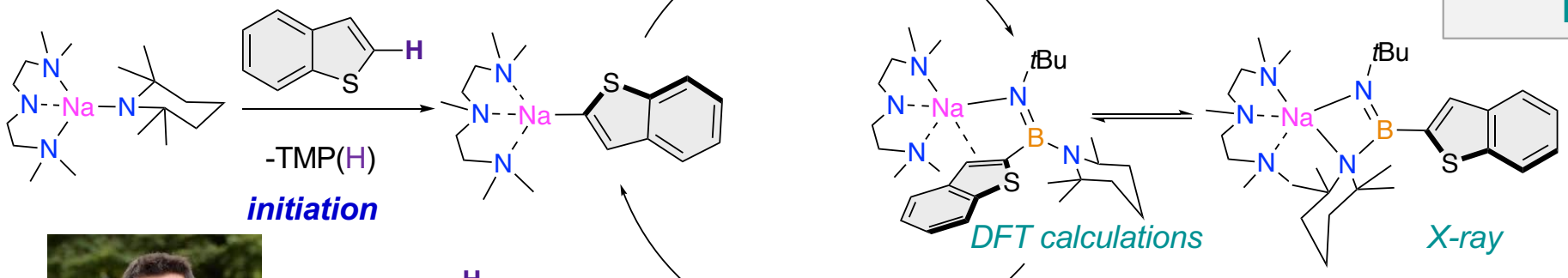
Mechanistic Understanding



Kinetic investigations
(initial rates and DFT simulation)
First order in [benzothiophene]
First order in [NaTMP]
Zeroth order in [Boron Trap]

ωB97XD:
6-31+G(d,p)/6-311+G(d,p)

Kinetic Isotopic Effect
KIE = 8.7



TMP(H) is not involved in catalytic cycle!



DFT calculations
Max Garcia-Melchor
(CIC energiGUNE, Spain)

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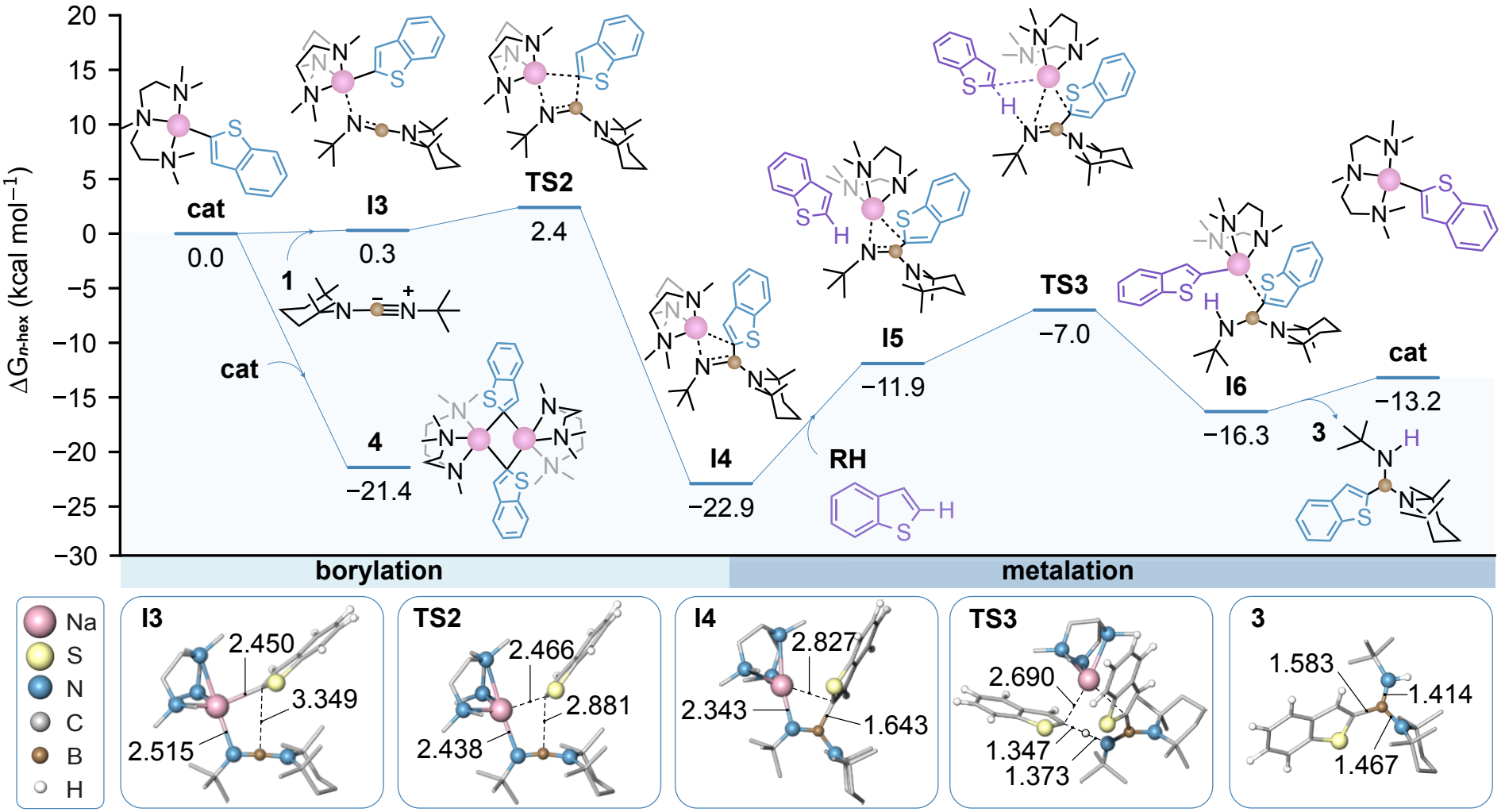
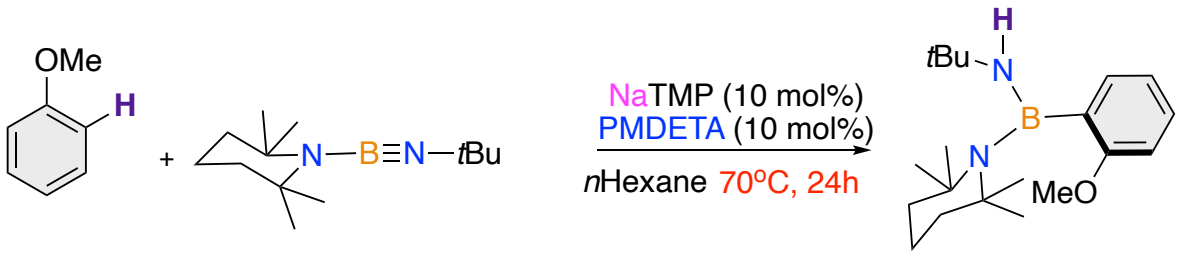
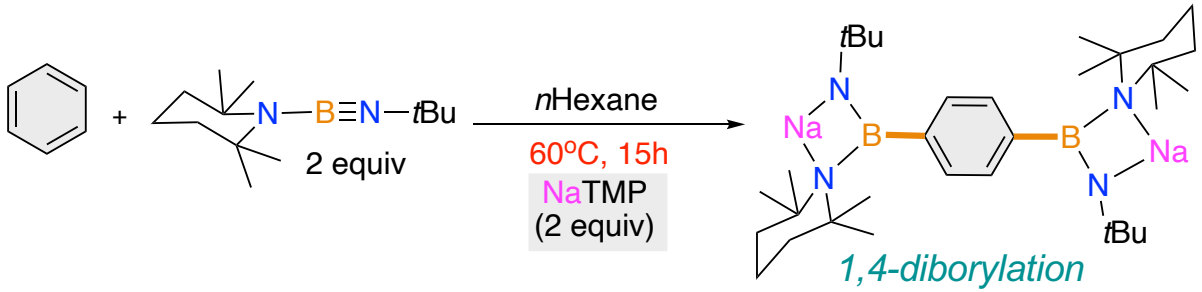
Mechanistic Understanding



Stoichiometric Polyborylation of Non-activated Arenes

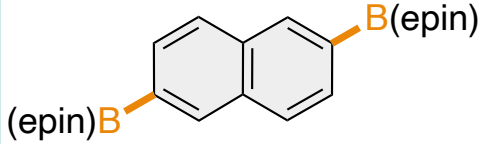


40%, 24h, 70°C
sluggish towards
non-activated arenes



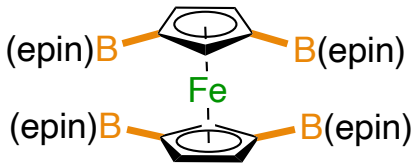
1,4-diborylation

2,6-diborylation



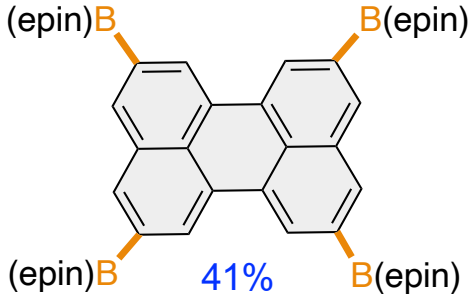
44%
(2 equiv NaTMP)

1,1',3,3'-tetraborylation



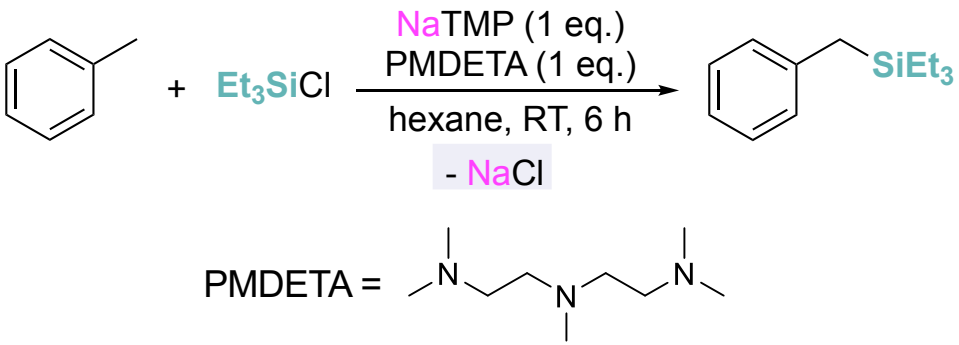
90%
(5 equiv NaTMP)

2,5,8,11-tetraborylation



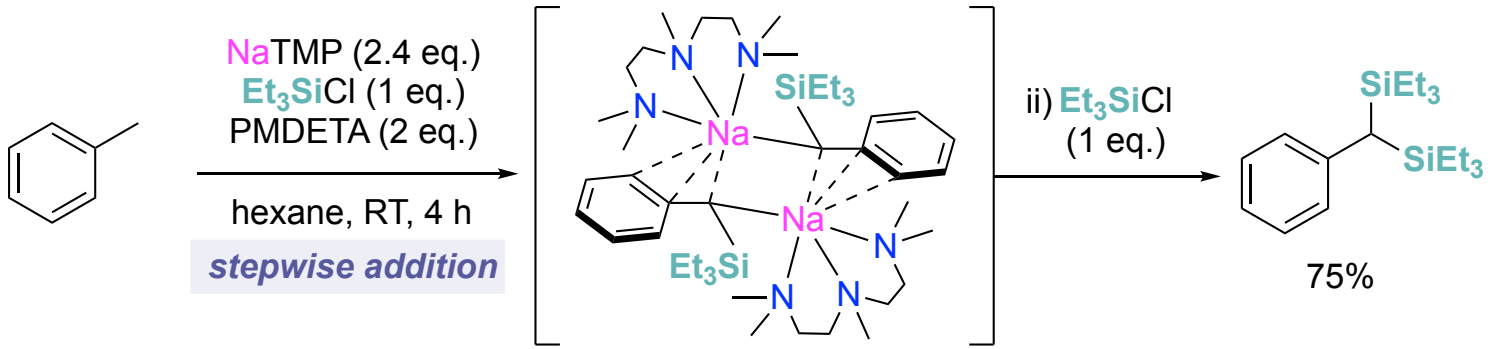
41%
(4 equiv NaTMP)

Sodium-mediated Silylation of Arenes and Heteroarenes



Deviation from the standard conditions	Yield [%]
None	73
LiTMP instead of NaTMP	18
$Na(CH_2SiMe_3)$ instead of NaTMP	0
Me_3SiCl instead of Et_3SiCl	0
10 mol% of PMDETA	**84**

Accessing gem-disilylation of toluene



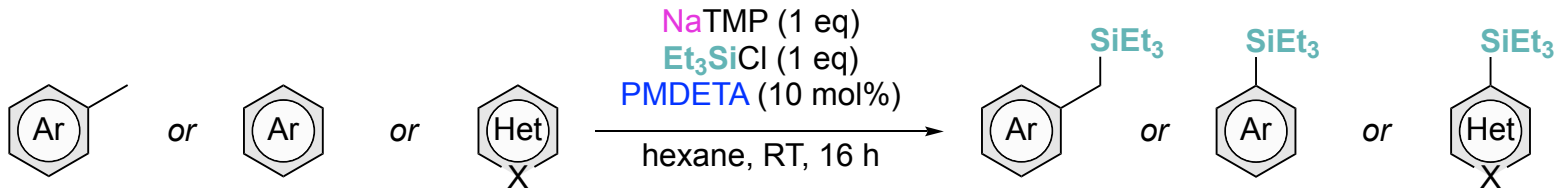
suggested by DOSY-NMR studies



David Sanchez-Roa

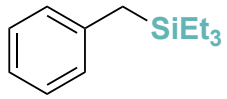
Angew. Chem. Int. Ed. **2026**, *65, e1774364*

Sodium-mediated Silylation of Arenes and Heteroarenes

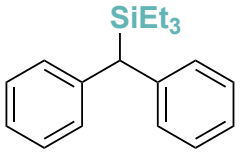


Benzylic C(sp^3)–H silylation

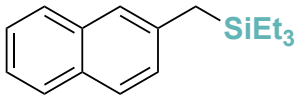
Gram-scale preparation (6 mmol)



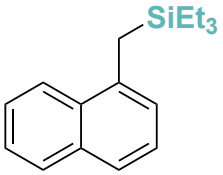
1a: 95% (1.17 g)



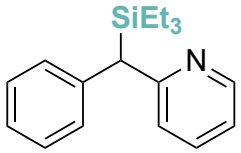
1b: 79%



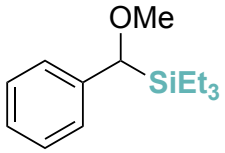
1c: 86%



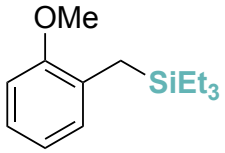
1d: 67%



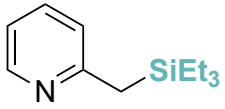
1e: 84%



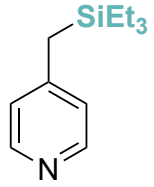
1f: 77%



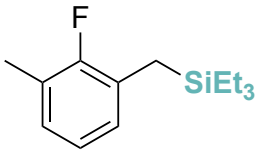
1g: 76%



1h: 71%



1i: 65%



1j: 68%



David Sanchez-Roa

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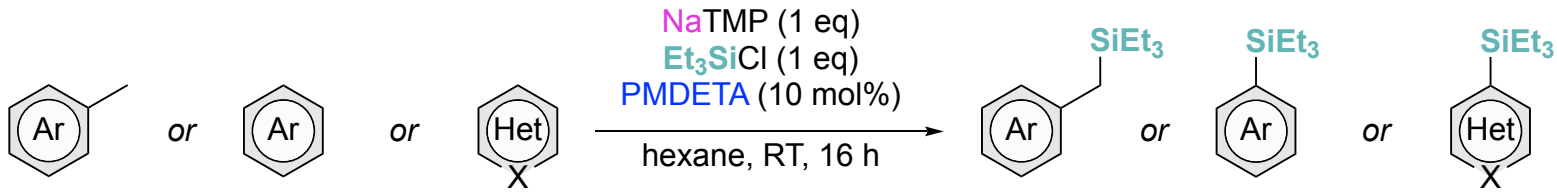
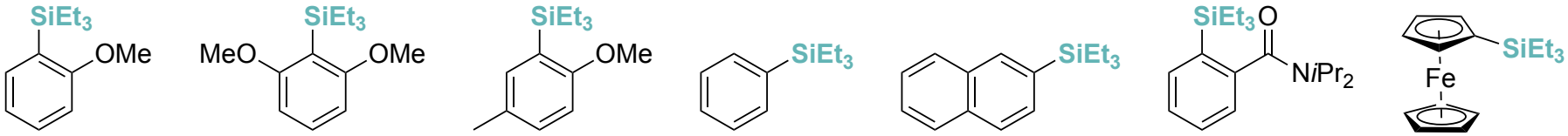
Sodium-mediated Silylation of Arenes and Heteroarenes



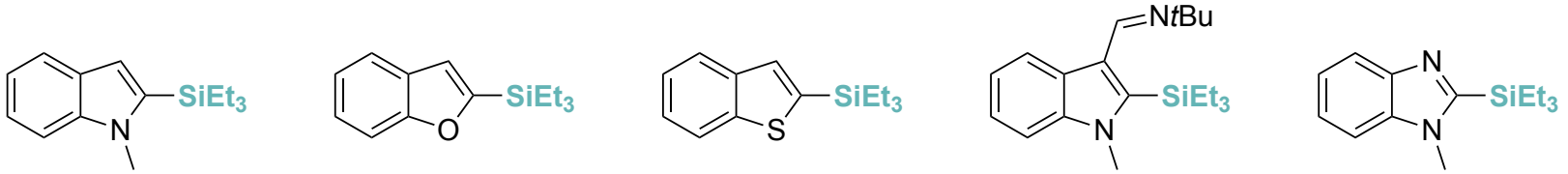
X = N, O, S **1** **2** **3**

Arenes: C(sp^2)–H silylation



2a: 75% **2b**: 71% **2c**: 71% **2d**: 91% **2e**: 71% **2f**: 72% **2g**: 62%

Heteroarenes: C(sp^2)–H silylation



3a: 92% **3b**: 91% **3c**: 87% **3d**: 83% **3e**: 40%

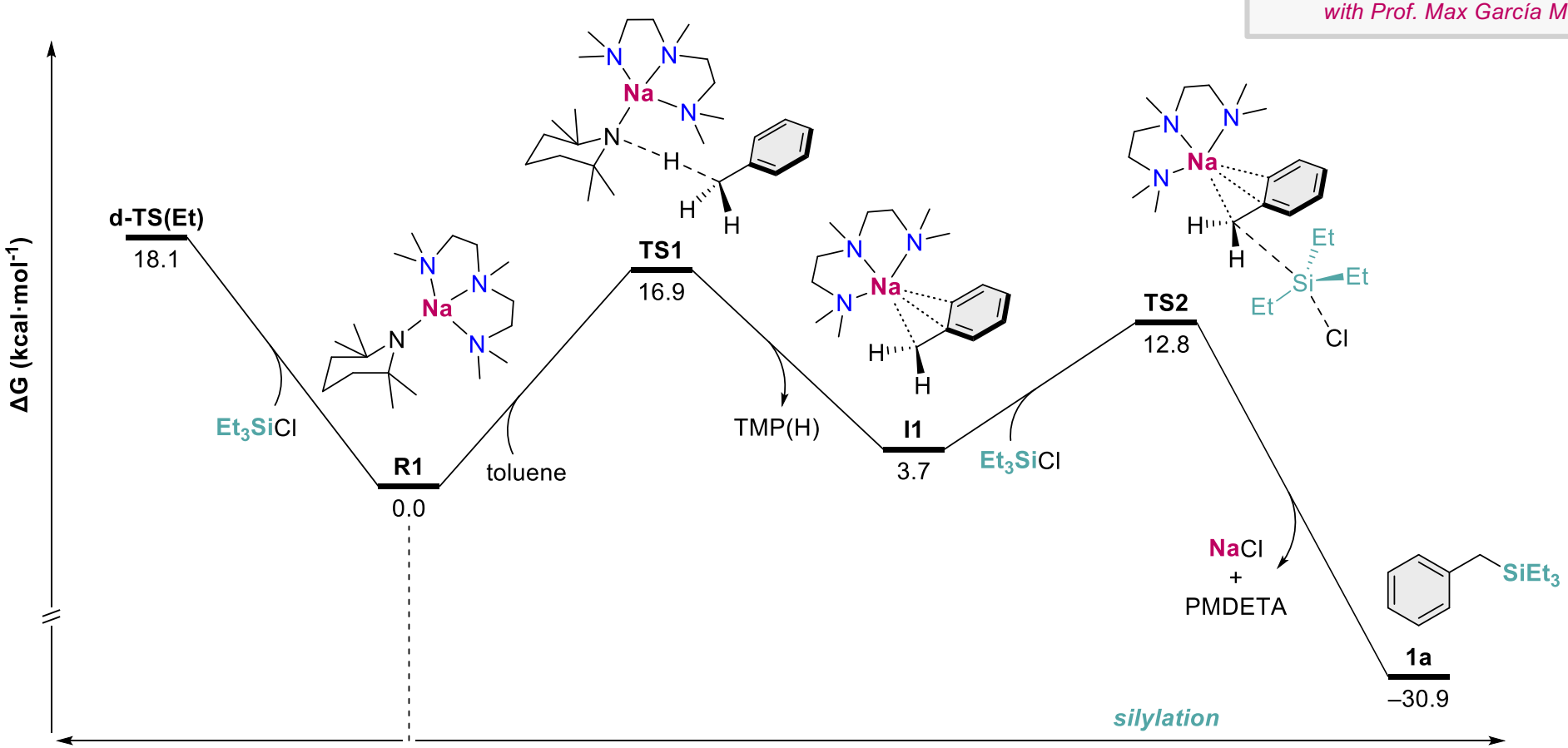


3f: 76% **3g**: 74% **3h**: 82% **3i**: 74%

Mechanistic Studies: DFT Silylation Pathway

UNIVERSITÄT BERN

Computational studies in collaboration with Prof. Max García Melchor



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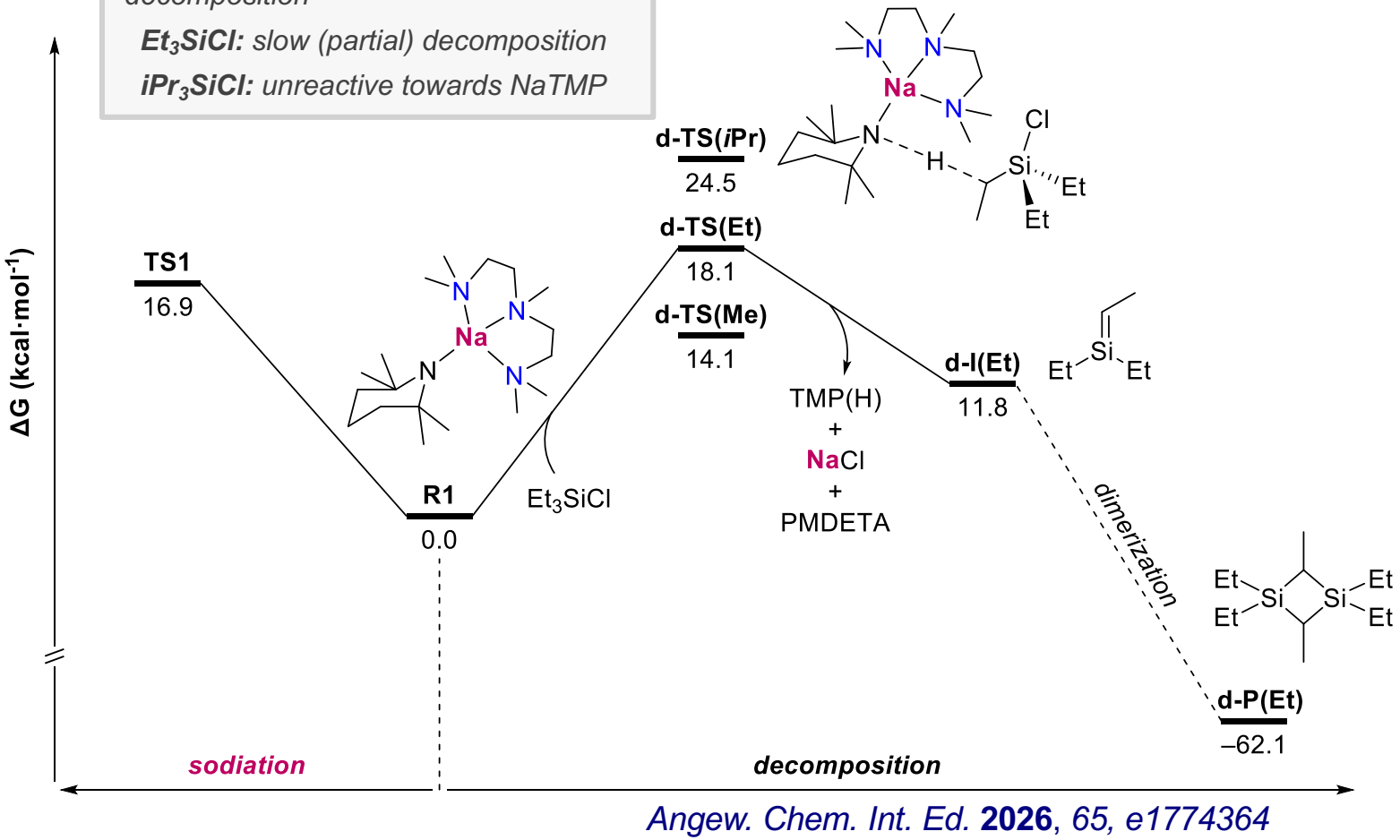
Mechanistic Studies: DFT Silylation Pathway

NMR monitoring experiments:

Me_3SiCl: *rapid and complete decomposition*

Et_3SiCl: *slow (partial) decomposition*

iPr_3SiCl: *unreactive towards NaTMP*



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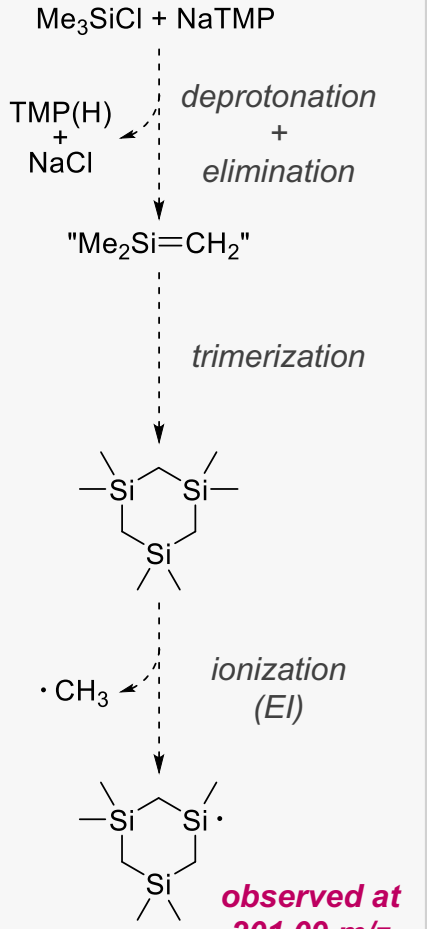
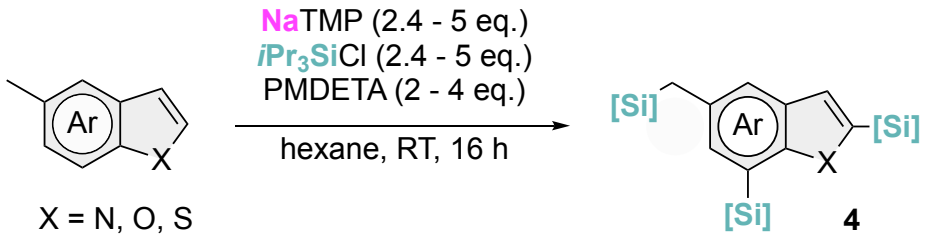
Decomposition studies (NMR + MS)



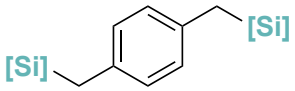
Stoichiometric Control in Multisilylation Reactions



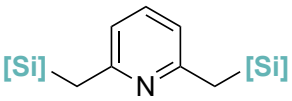
X = N, O, S

4

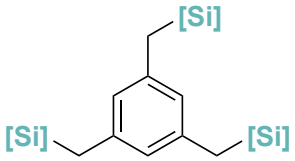
Benzylic C(sp^3)–H multisilylation



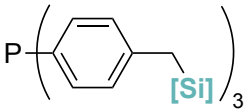
4b: 97%



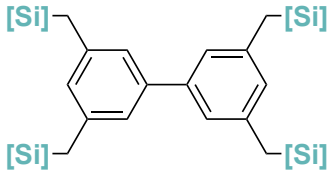
4c: 81%



4d: 96%

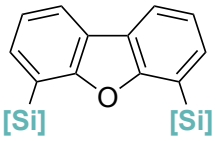


4e: 81%

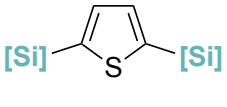


4f: 93%

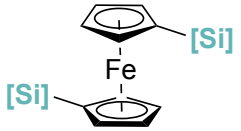
(Hetero)arenes: C(sp^2)–H multisilylation



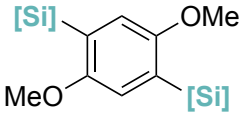
4g: 95%



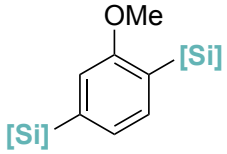
4h: 93%



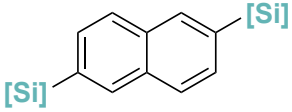
4i: 88%



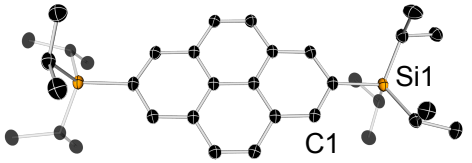
4j: 98%



4k: 83%

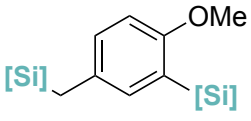


4l: 95%

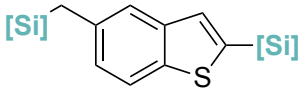


4m: 59%

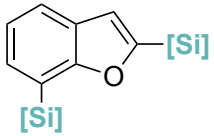
Orthogonal multisilylation



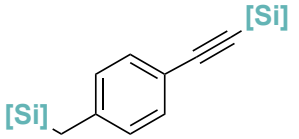
4n: 97%[b]



4o: 97%



4p: 74%



4q: 83%

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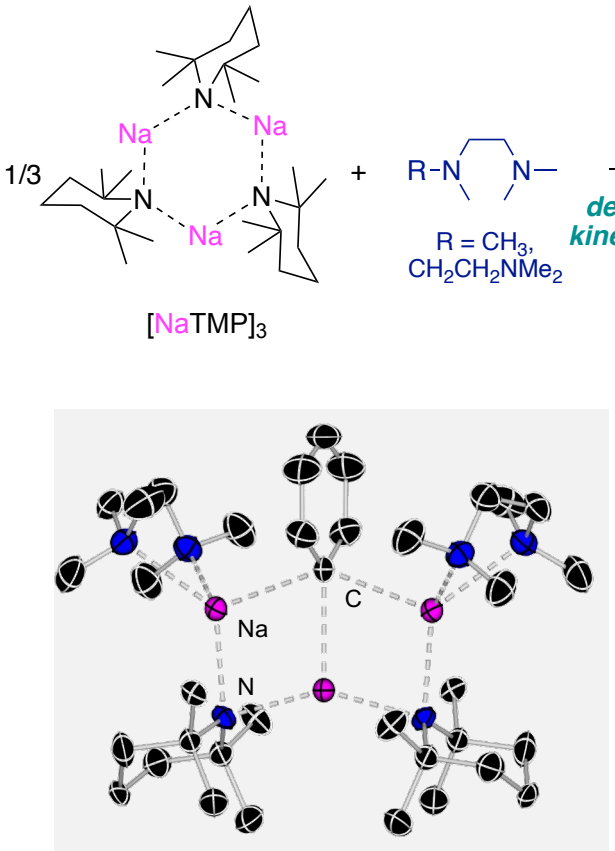
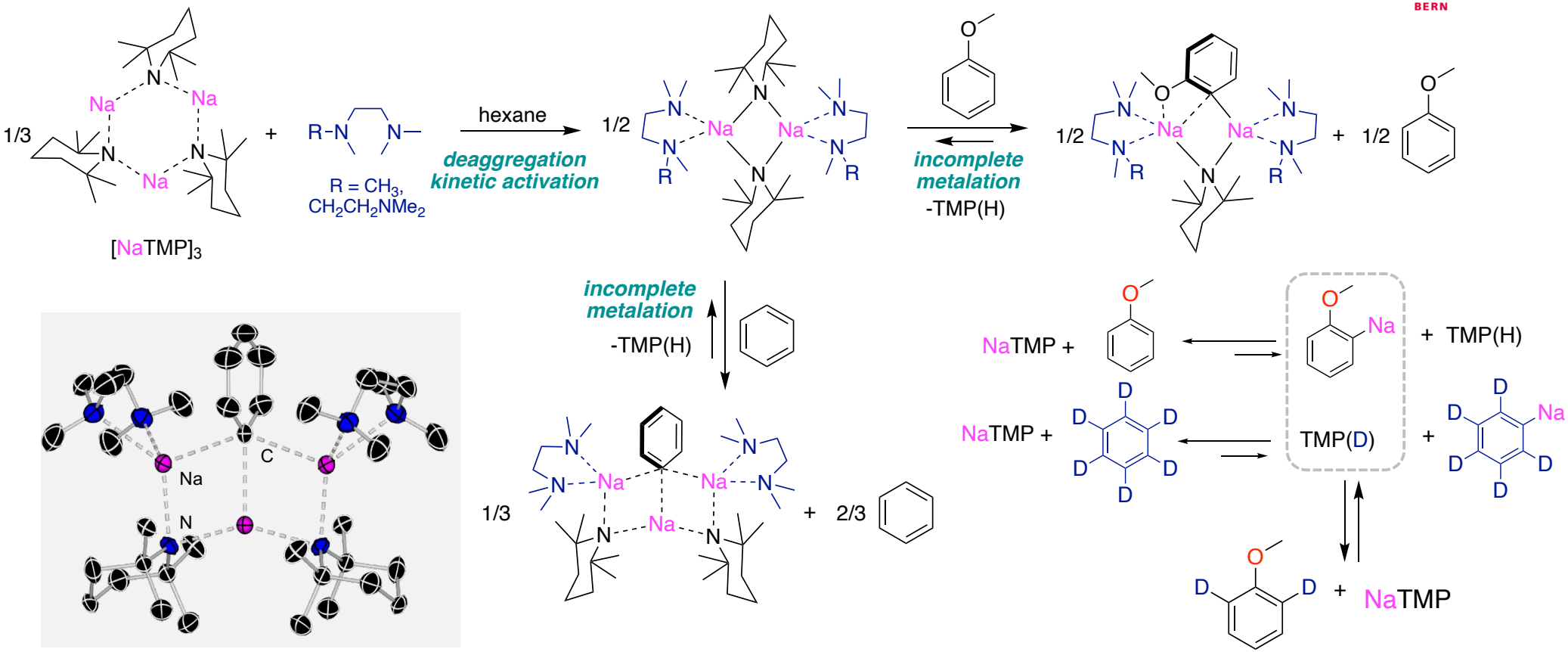
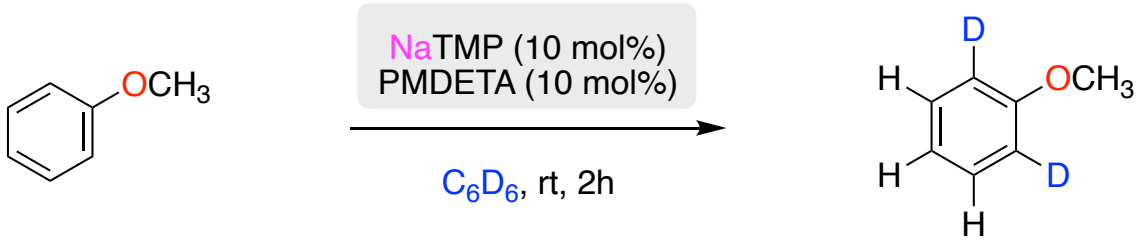
Metalation of Arenes with NaTMP: an Equilibrium



Metalation of Arenes with NaTMP: an Equilibrium

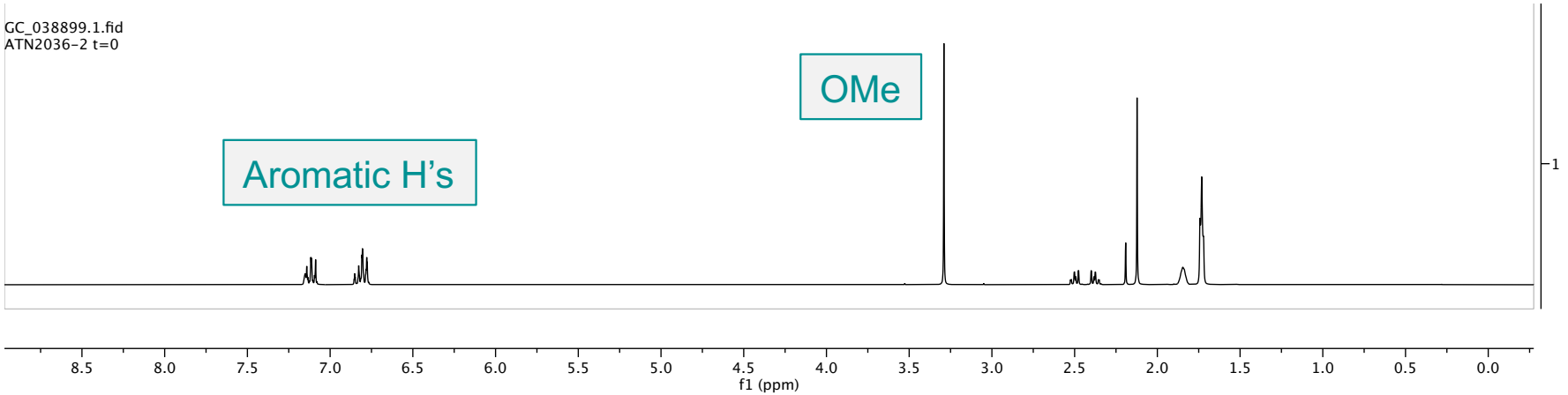


Benzene C-H Deprotonation for Isotopic Incorporation

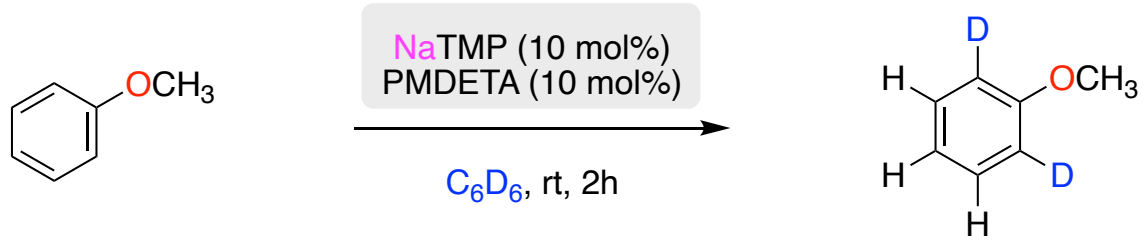


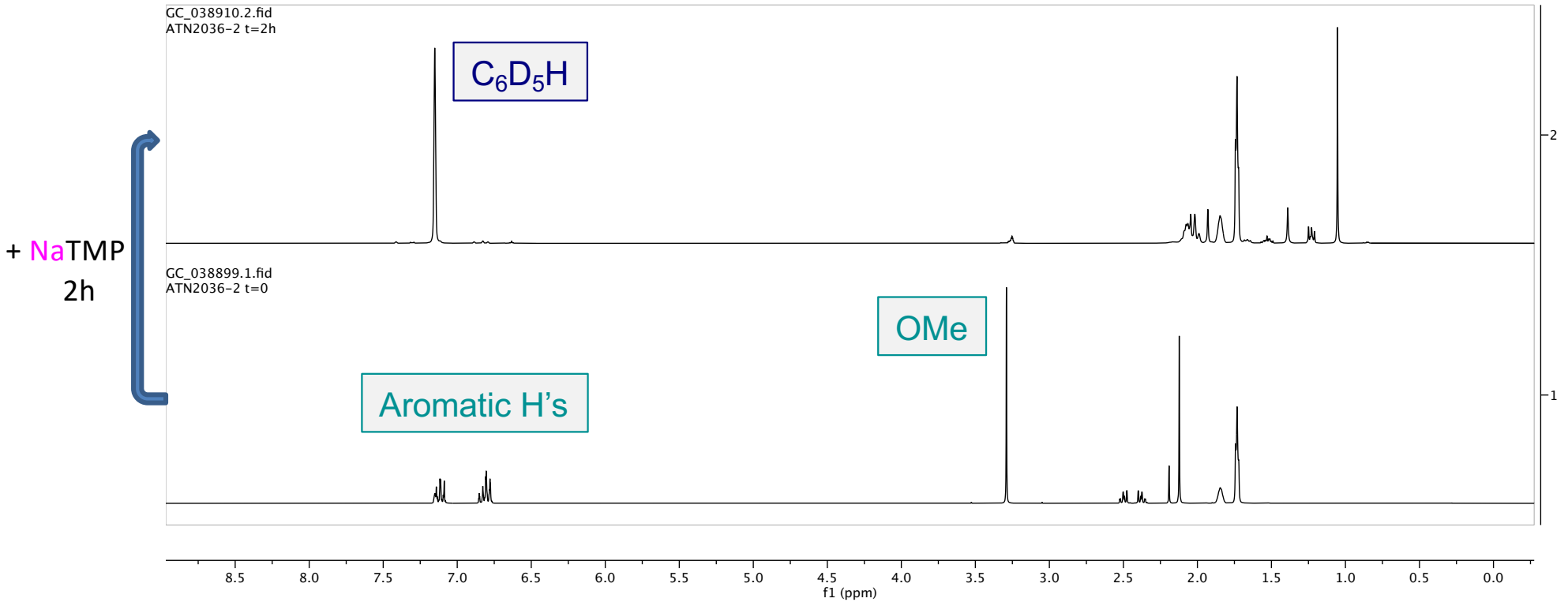


Andreu Tortajada

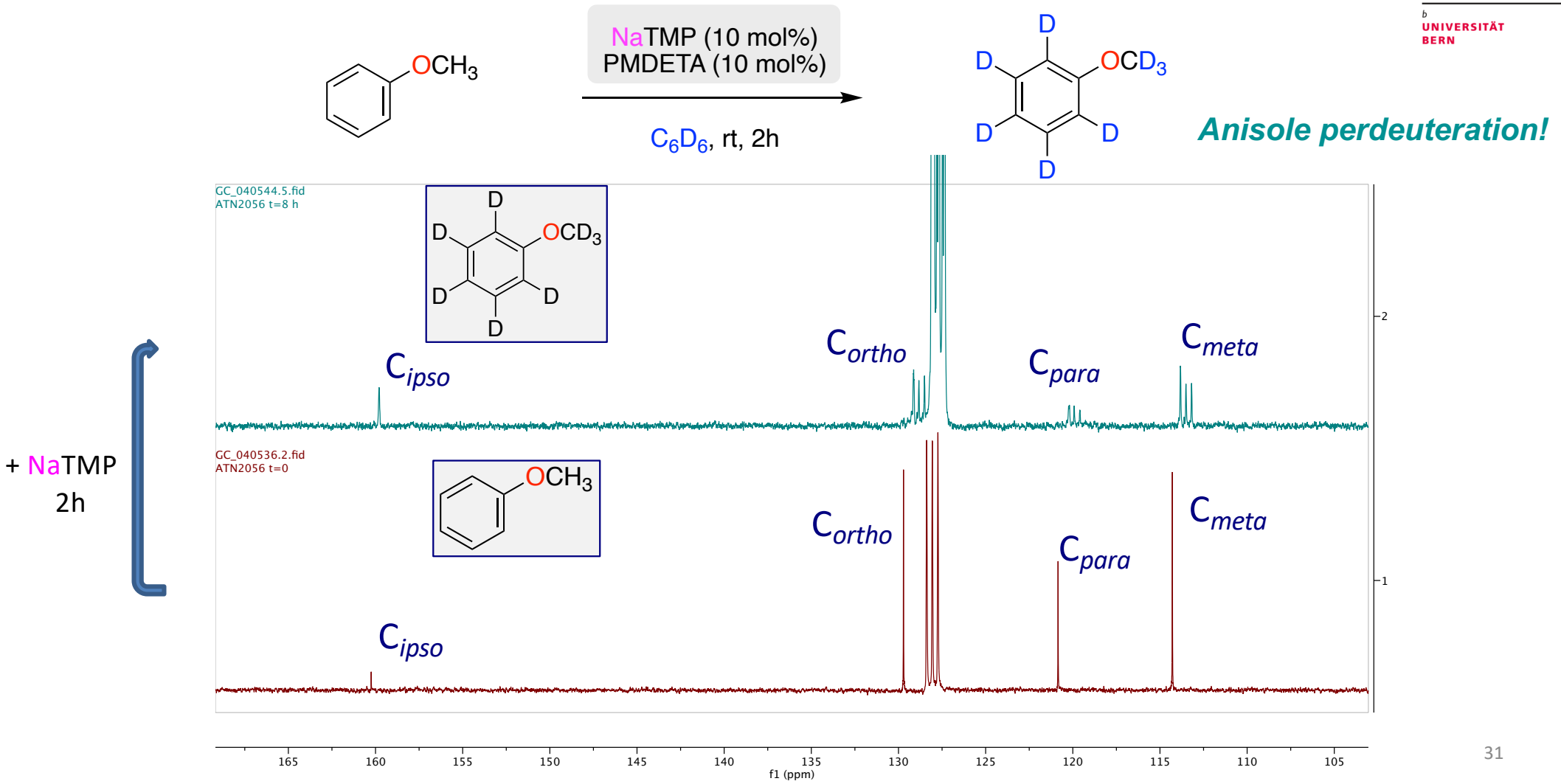


Benzene C-H Deprotonation for Isotopic Incorporation

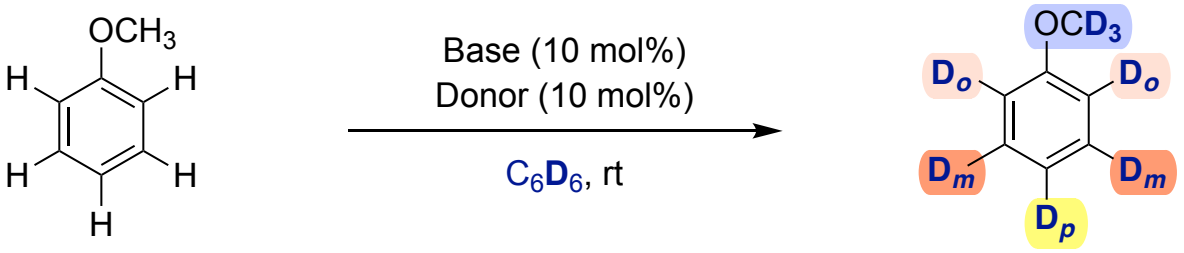




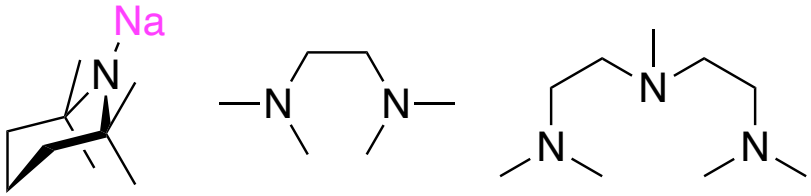
Benzene C-H Deprotonation for Isotopic Incorporation



Assessing Base and Donor Effects on the Deuteration of Anisole

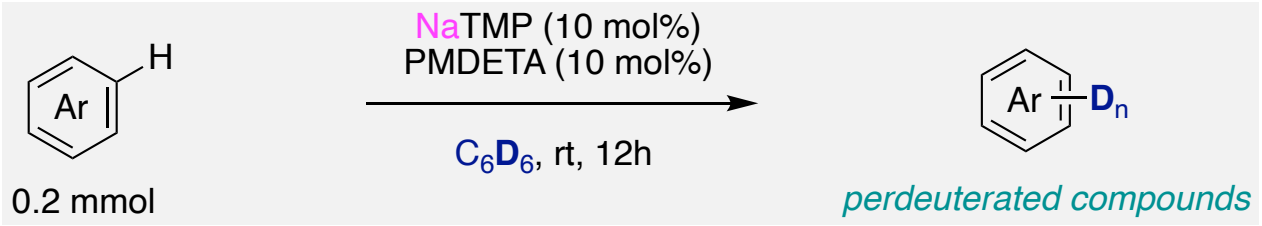


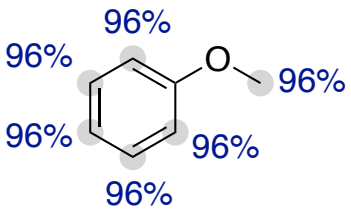
Base	Donor	Time	Degree of deuteration /%			
			D_o	D_m	D_p	OCD_3
NaTMP	PMDETA	4h	>95	>95	>95	>95



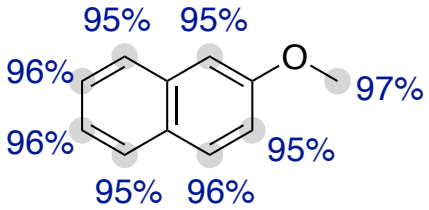
NaTMP TMEDA PMDETA

Substrate Scope of NaTMP/PMDETA Catalysed HIE

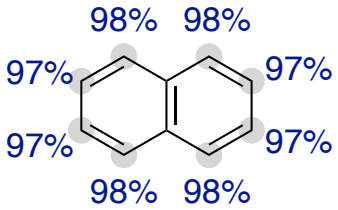




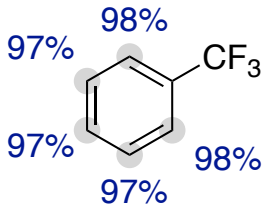
1a-d_8



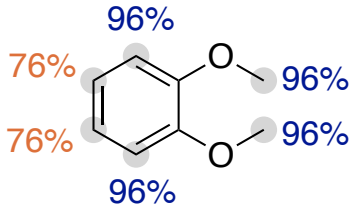
1b-d_{10}



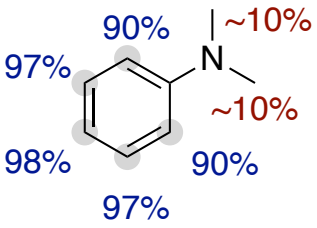
1c-d_8



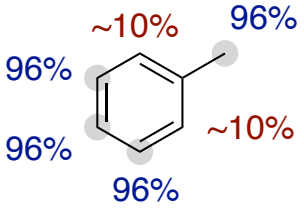
1d-d_5



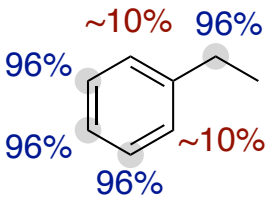
1e-$d_{11/12}$



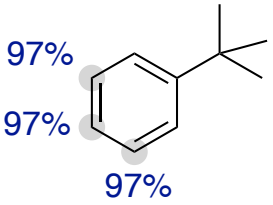
1f-d_5



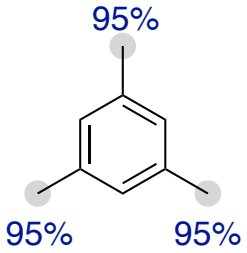
1g-d_6



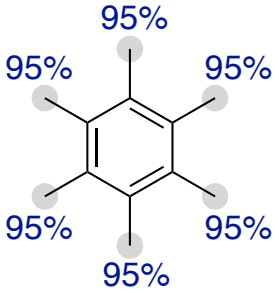
1h-d_5



1i-d_3



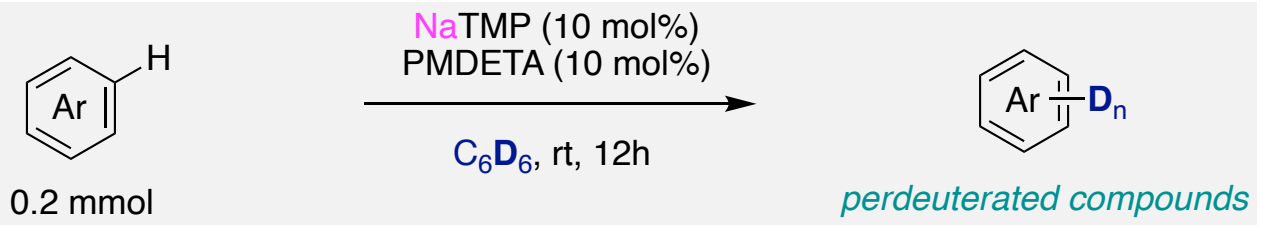
1j-d_9

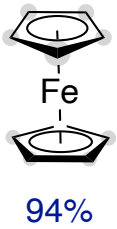


1k-d_{18}

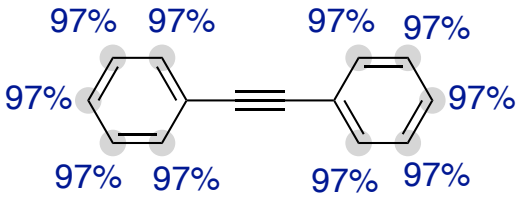
J. Am. Chem. Soc. **2022**, *144*, 20237; *Cat. Sci. Tech.* **2023**,*13*, 4919

Substrate Scope of NaTMP/PMDETA Catalysed HIE

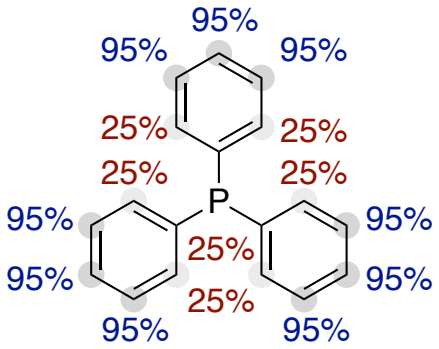




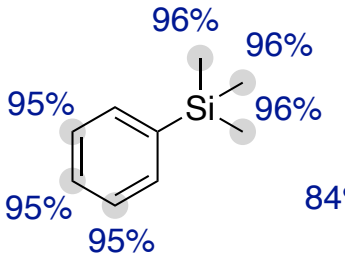
1l-d_{10}



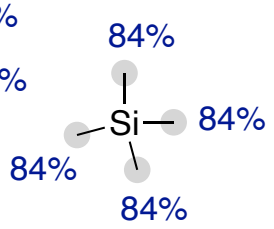
1m-d_{10}



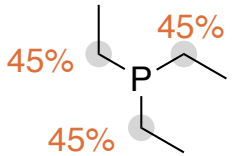
1n-$d_{9/10}$



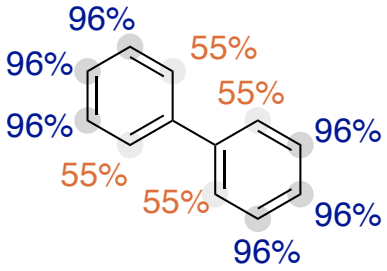
1o-d_{12}



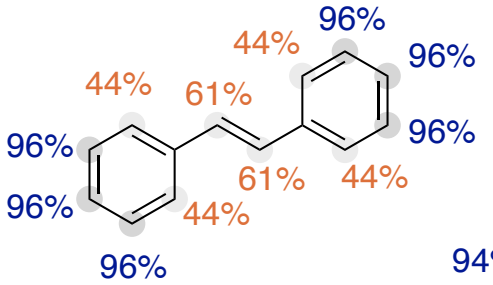
1p-d_{12}



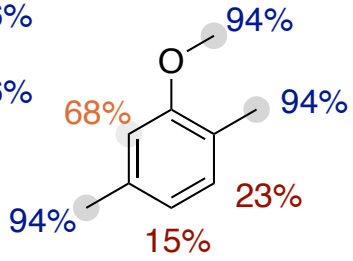
1q-d_3/d_6



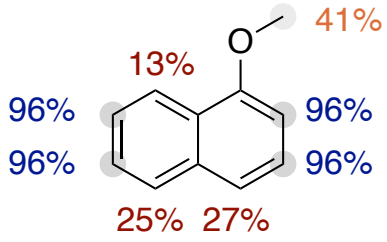
1r-d_6/d_{10}



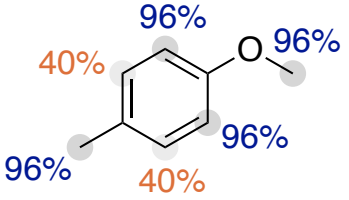
1s-d_8



1t-d_{10}



1u-d_4/d_7



1v-d_8/d_{10}

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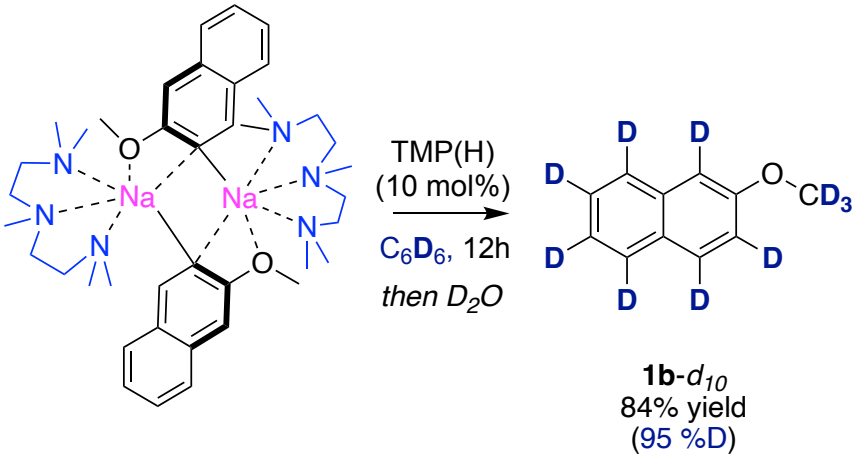
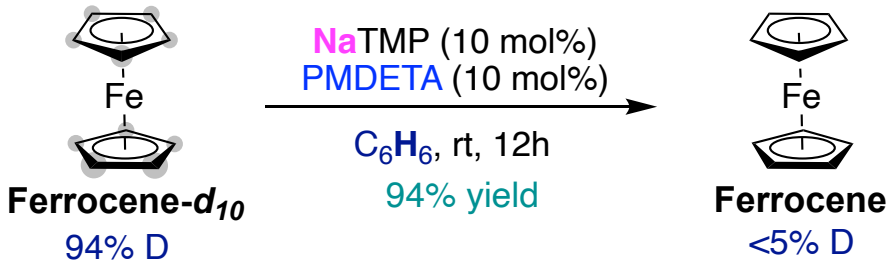
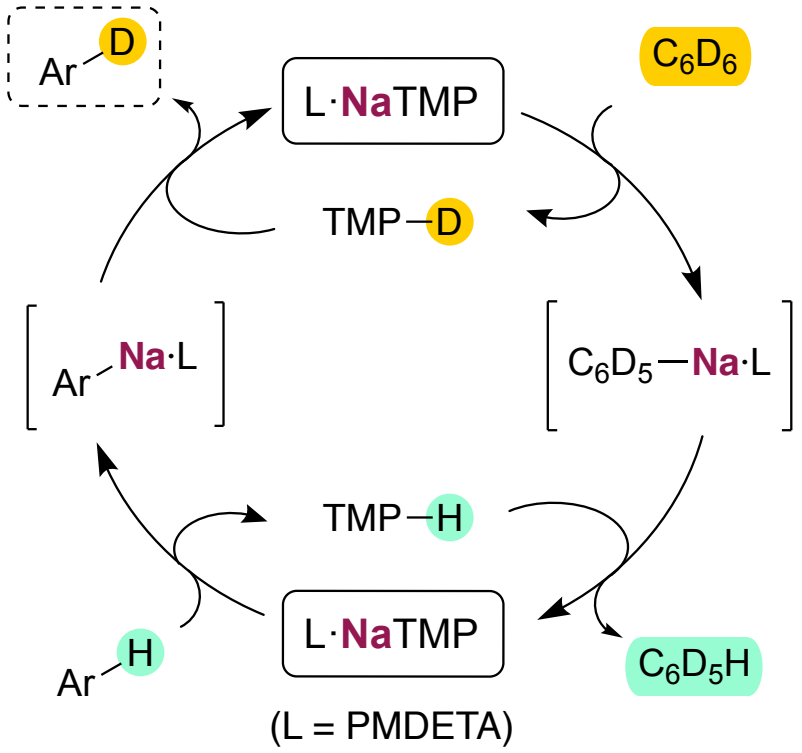
Investigating the Role of NaTMP/TMP(D)



no apparent deuteration without TMP

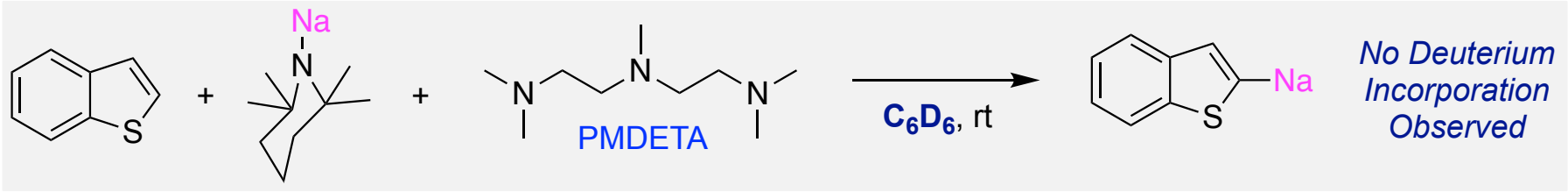
NaTMP / TMP(D) as a shuttle for isotopic exchange!

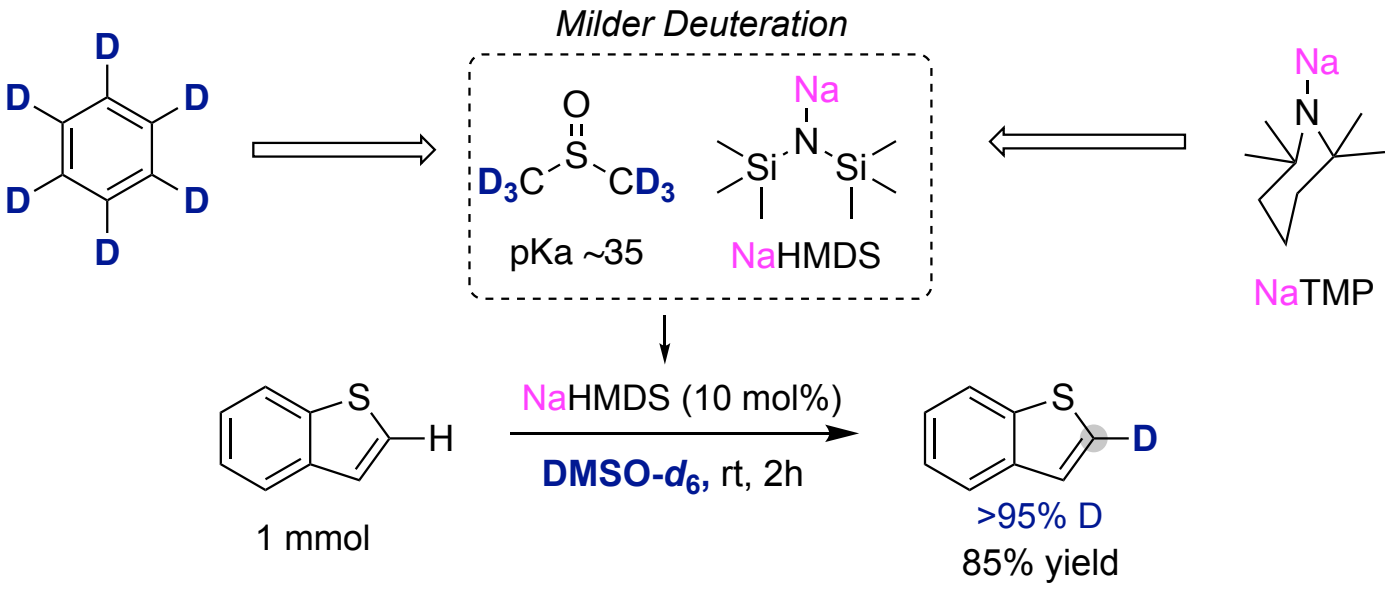




J. Am. Chem. Soc. **2022**, *144*, 20237; *Cat. Sci. Tech.* **2023**,*13*, 4919

Redesign of the Deuteration Platform





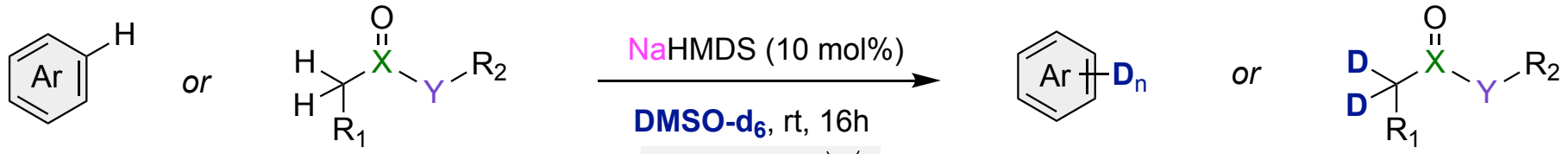


Andreu Tortajada

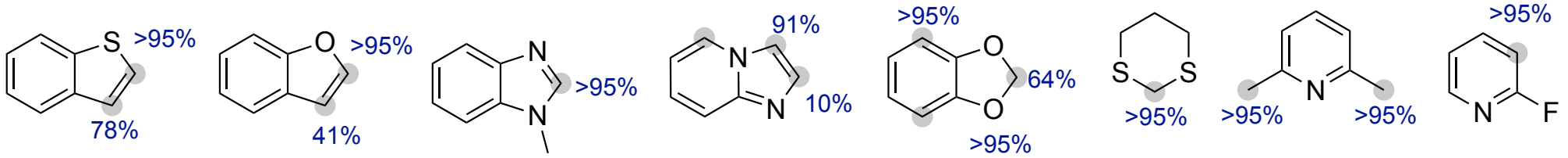


Melina Tschopp

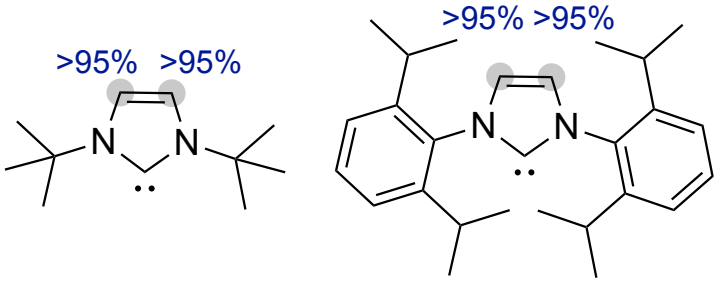
Redesign of the Deuteration Platform



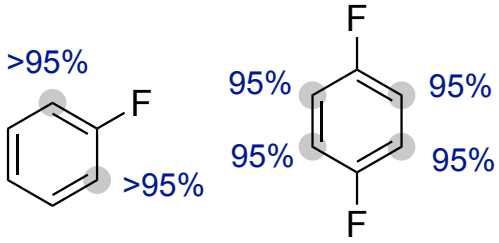
Heterocycles



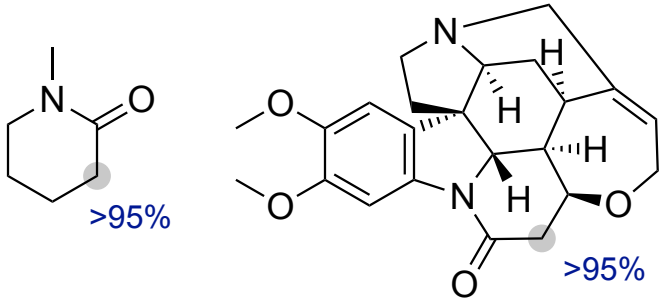
NHCs



Fluoroarenes



Amides



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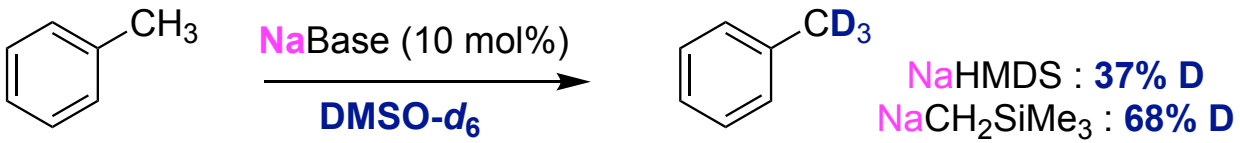
Brucine (alkaloid)

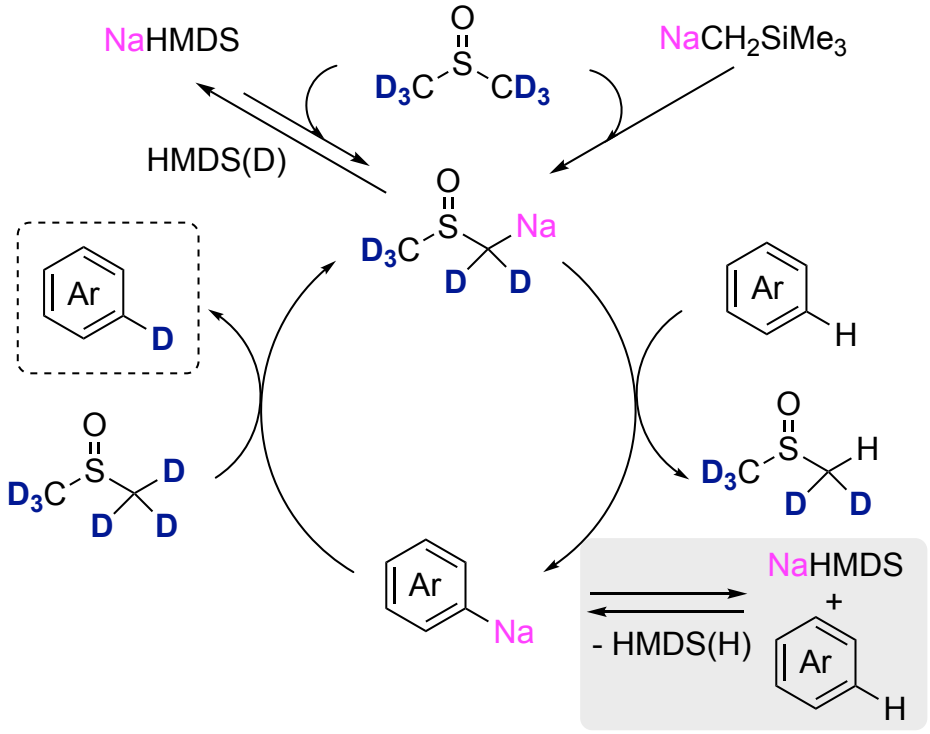
Redesign of the Deuteration Platform

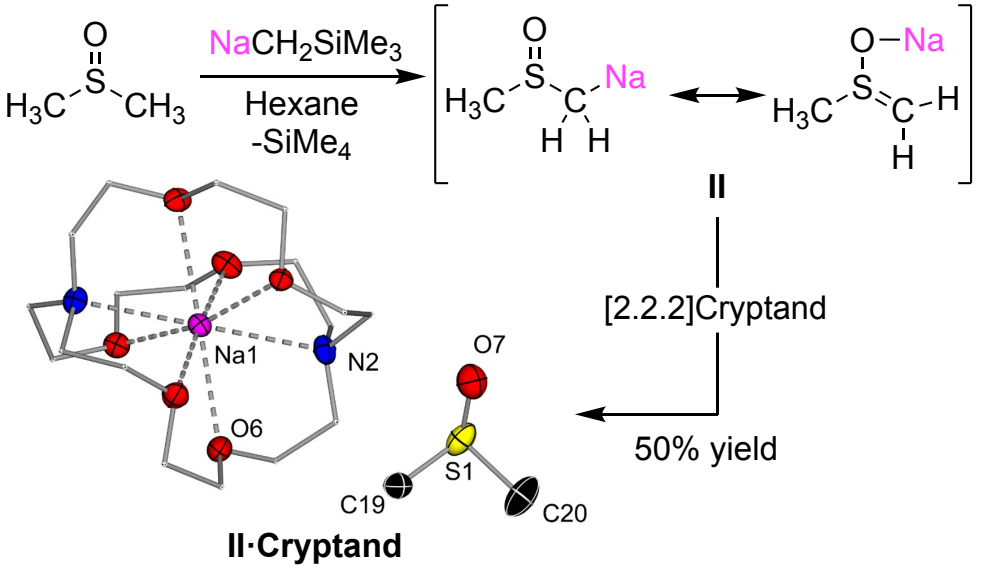


NaHMDS : **37% D**
$NaCH_2SiMe_3$: **68% D**

HMDS(H) is **not needed** for the HIE
$NaCH_2SiMe_3$ is a **more poweful** catalyst!

Proposed mechanism





catalytically competent

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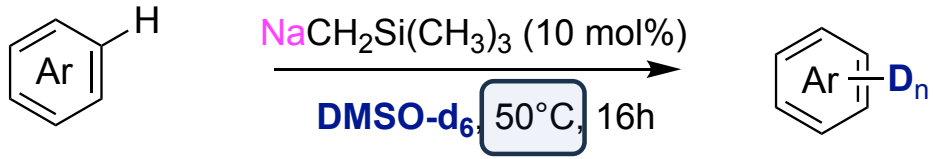
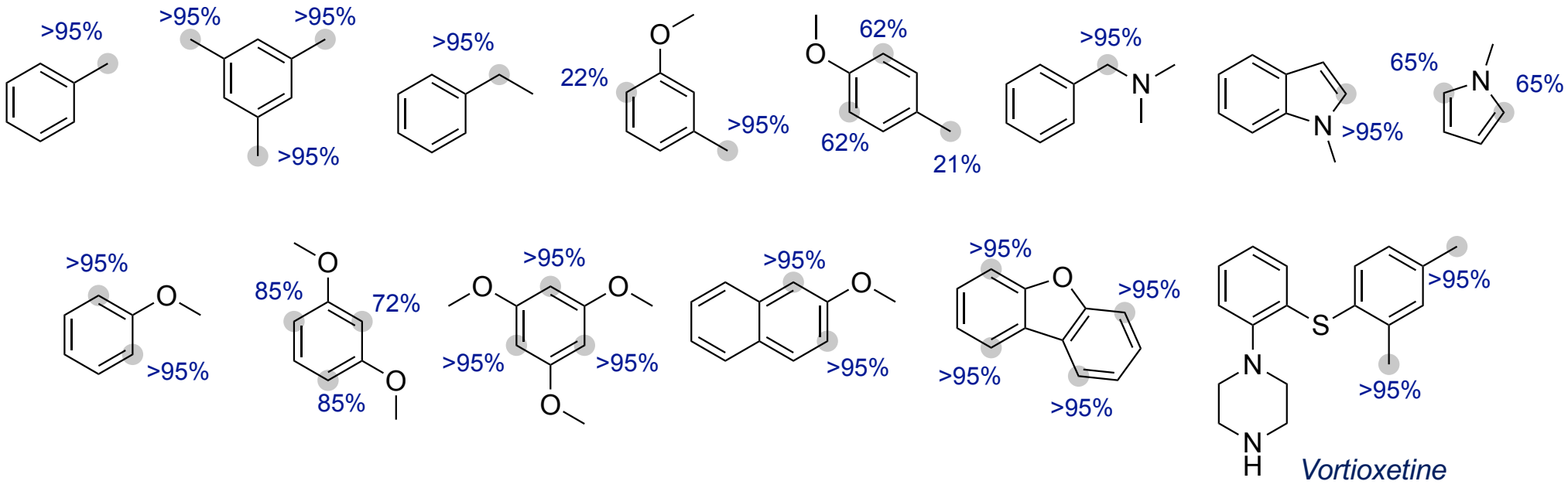
Redesign of the Deuteration Platform



16 examples, regioselective deuteration



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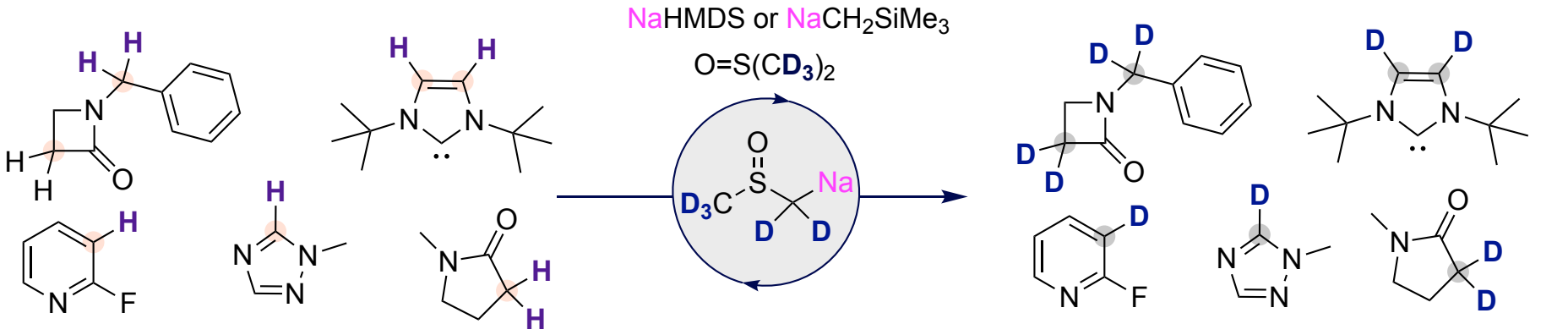
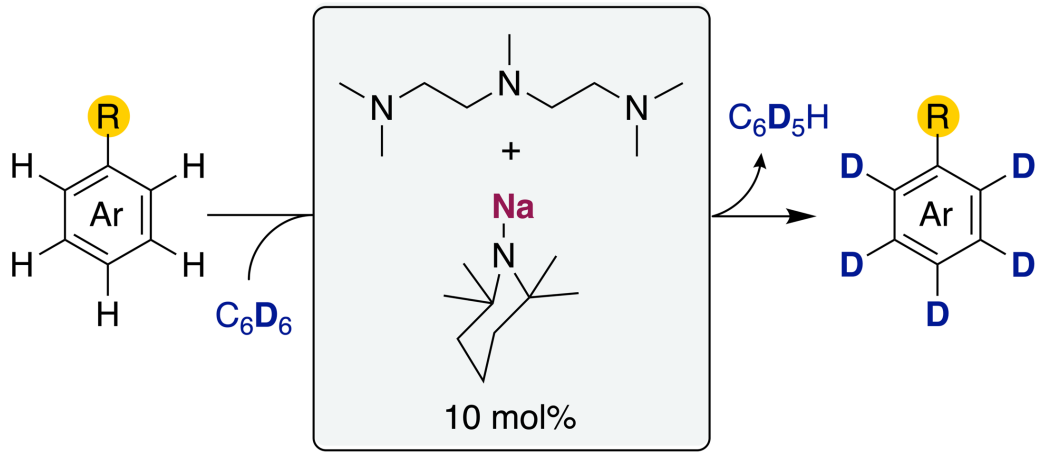
Two Complementary Na-catalysed HIE Methods



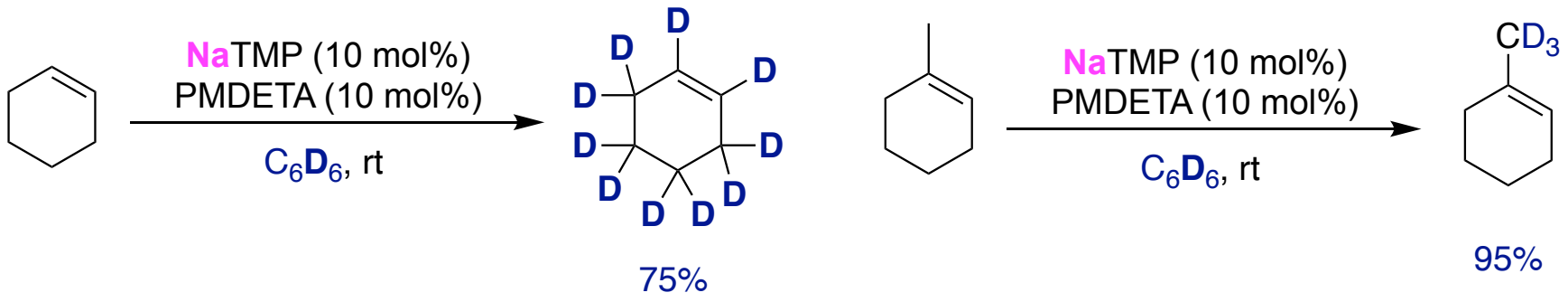
✔ *Simple Reagents* ✔ *Mild Conditions* ✔ *Mechanistic Understanding* ✔ *Selective Deuteration*

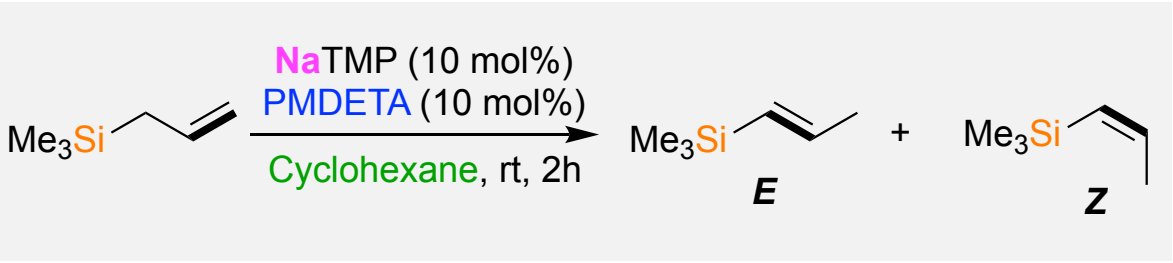


- ✔ *Efficient Perdeuteration*
- ✔ *Mild Conditions*
- ✔ *Mechanistic Understanding*
- ✔ *Non-activated Substrates*

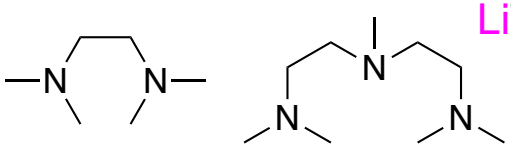
Deuteration of Cyclohexane: A Gateway for Alkene Isomerisation

deuteration and isomerisation





86%, 90 min; 94:6 *E:Z* selectivity



TMEDA

PMDETA

LiTMP/PMDETA, 7%

NaTMP/TMEDA, 61% (81:19 *E:Z*)

alkali-metal and Lewis donor effects!

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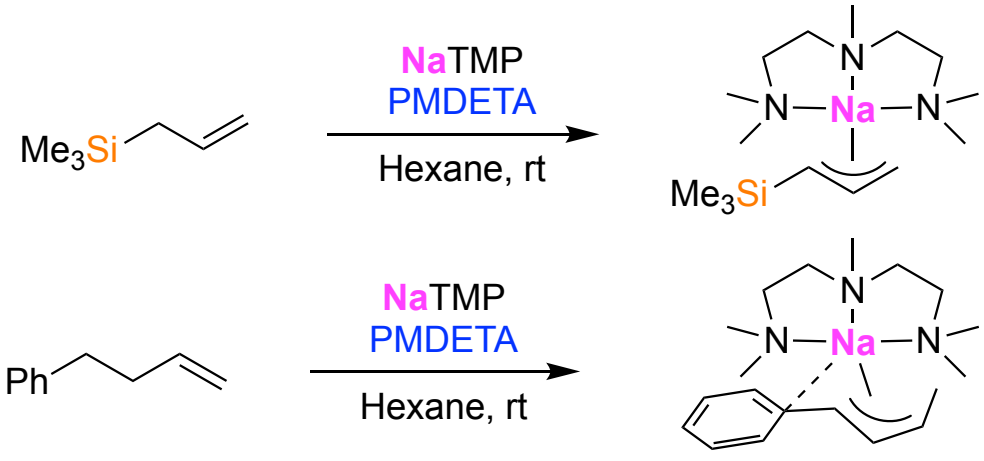
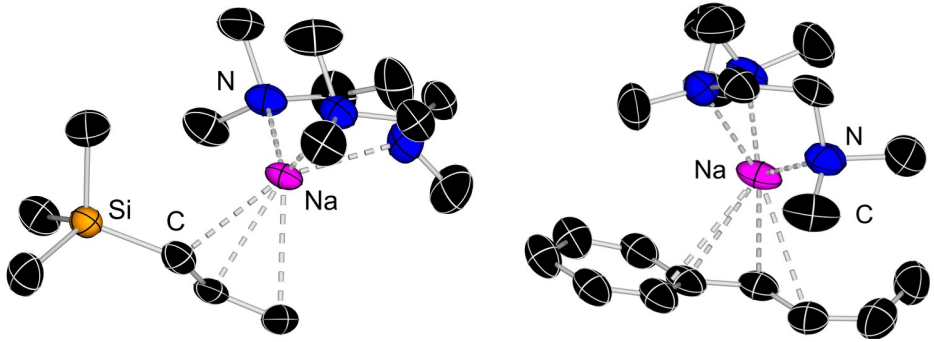
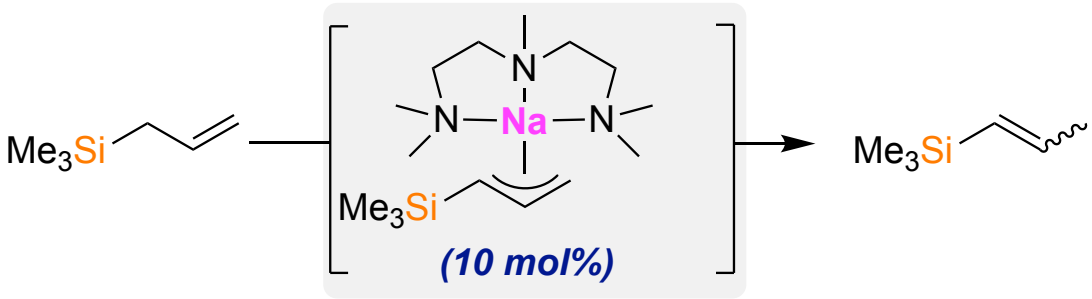
Mechanistic investigations

Isolation of π-allyl intermediate







TMP(H) accelerating effect!

88%, **3 days**

86:14 *E:Z* selectivity

---

vs NaTMP (PMDETA) cat:

86%, **90 min**

94:6 *E:Z* selectivity

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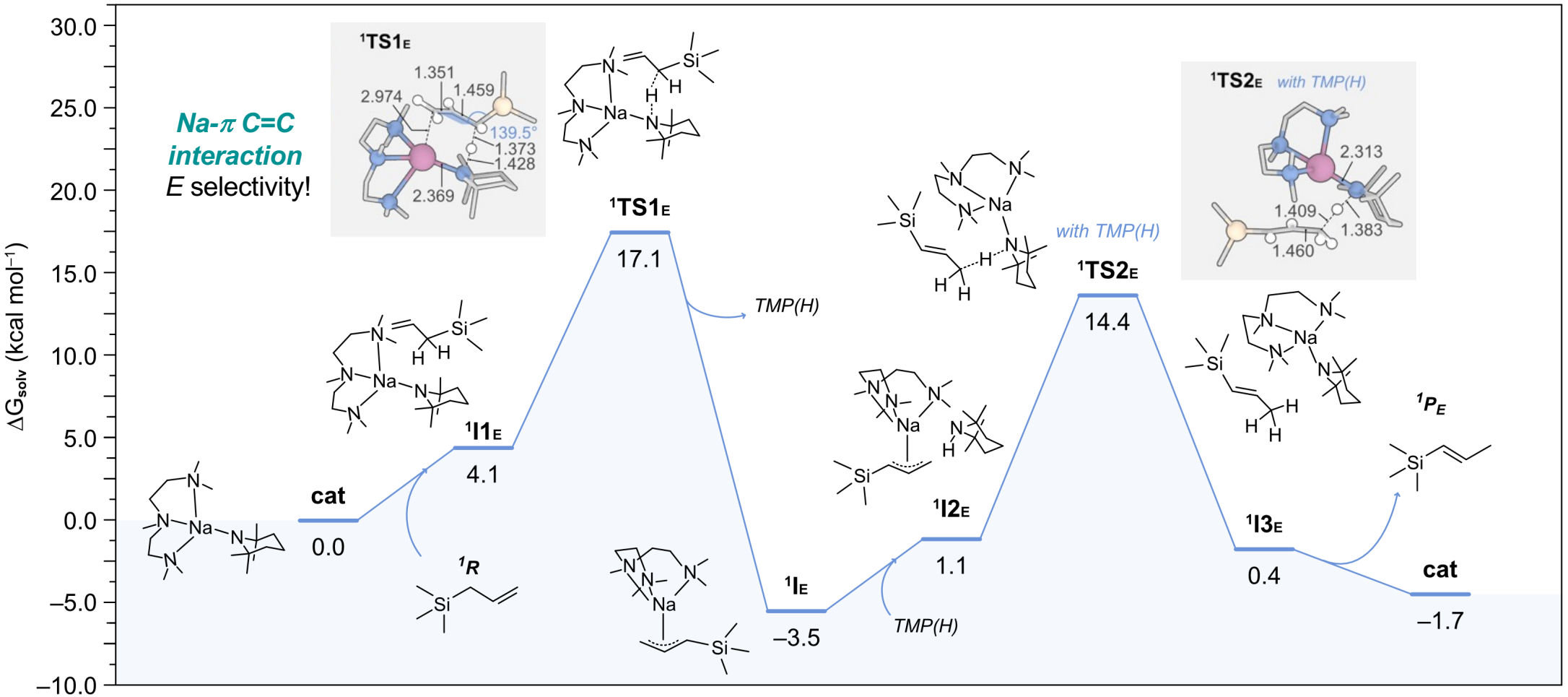
Sodium Catalysed Alkene Isomerisation



ωB97XD:6-31+G(d,p)/6-311+G(d,p)

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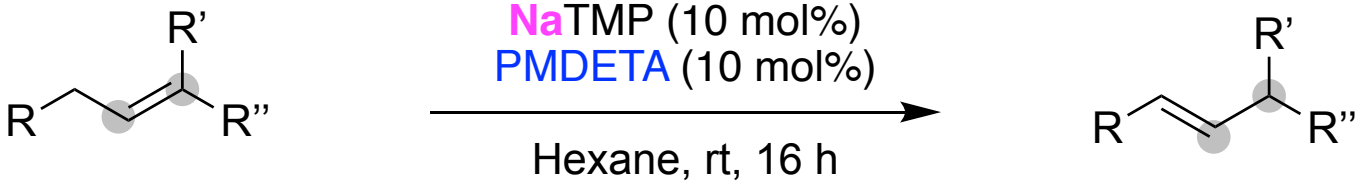
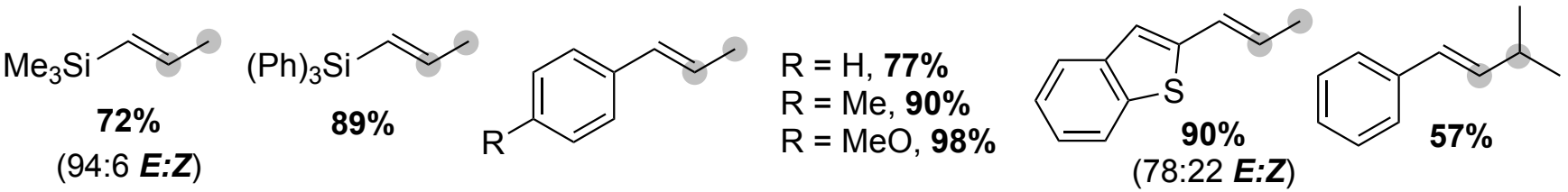
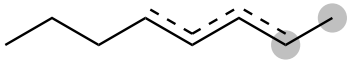
Sodium Catalysed Alkene Isomerisation





Limitation:



Mixture of isomers
100% conv.

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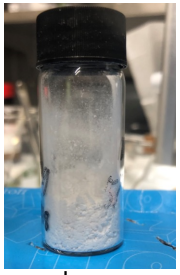
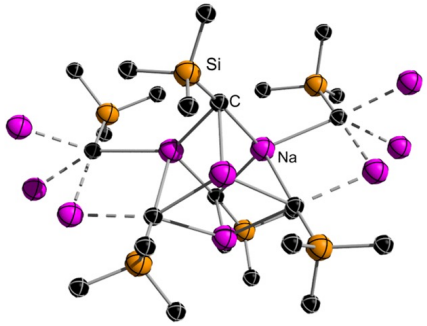
Highly Reactive Hydrocarbon Soluble Alkylsodium Reagents



$NaCH_2SiMe_3$



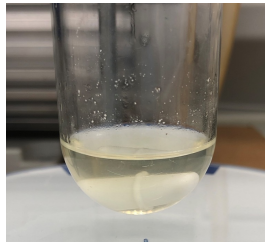
- thermally stable (lack of of β-Hs)
- $SiMe_3$ can enhance solubility
- highly aggregated structure $[\{Na(CH_2SiMe_3)\}_4]_n$

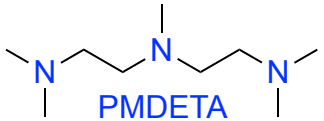
T. Shun et al, *Chem Commun.* **1993**, 1386

hexane



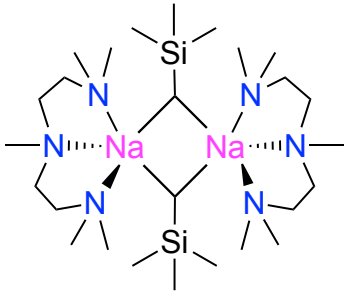
PMDETA





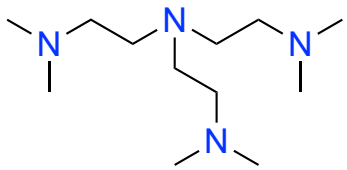
hexane, RT

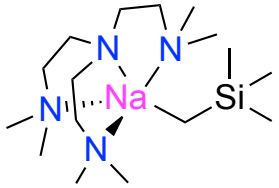
$[\{Na(CH_2SiMe_3)\}_4]_n$

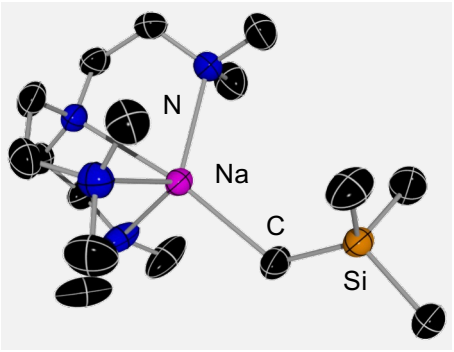


^{1}H, ^{13}C and ^{1}H DOSY NMR

Me_6-TREN hexane, RT







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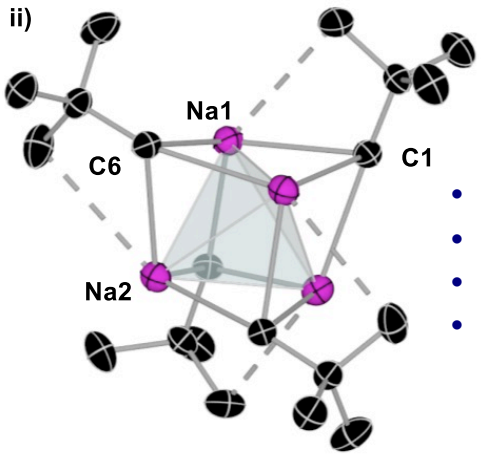
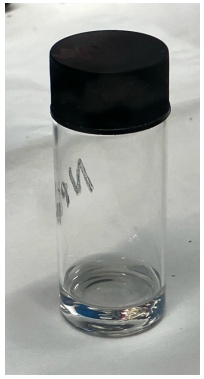
David Anderson

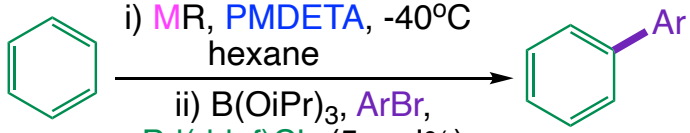
Donor-free hydrocarbon soluble alkyl sodium



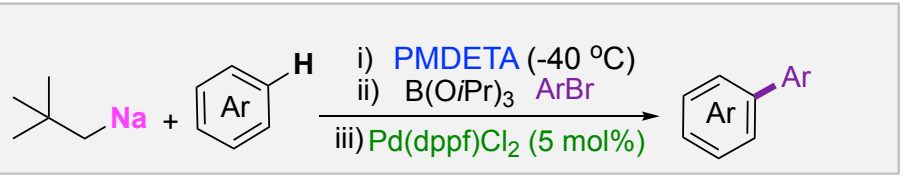
$[NaCH_2tBu]_4$

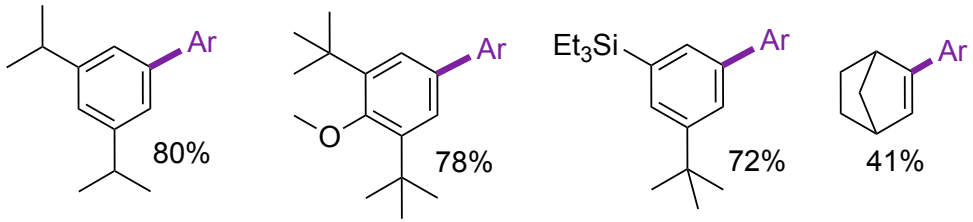
- discrete tetramer
- stabilised by dispersion
- soluble in hexane
- thermally stable





MR	Yield (%)
$NaCH_2SiMe_3$	21
$NaCH_2tBu$	**83**
$LiCH_2tBu$	12
$LiCH_2tBu$ + NaOtBu	49

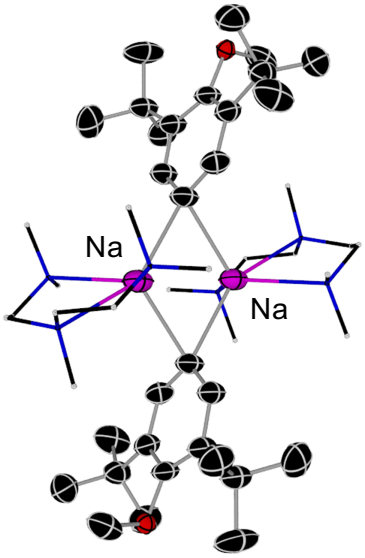




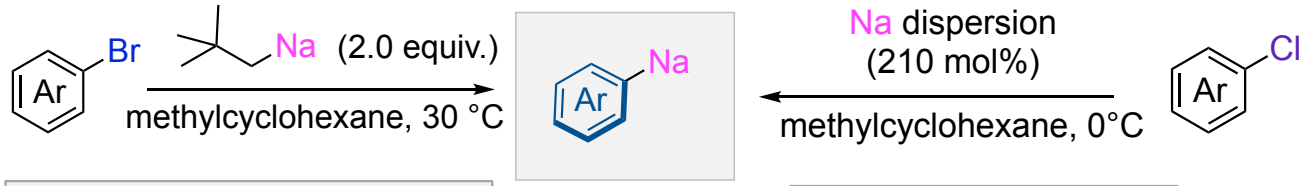
***meta*-regioselectivity**

C-H metalation of **non-activated** substrates

in preparation



Making Organosodium Chemistry Even More Sustainable



Halogen–sodium exchange of aryl bromides

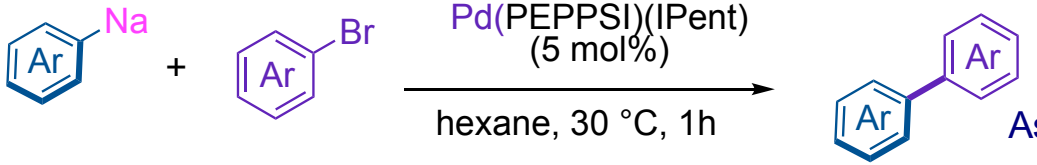
Reductive sodiation of aryl chlorides



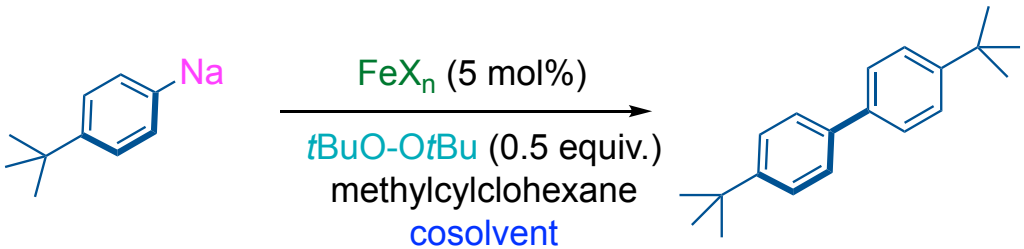
Laurean Ilies



Sobi Asako

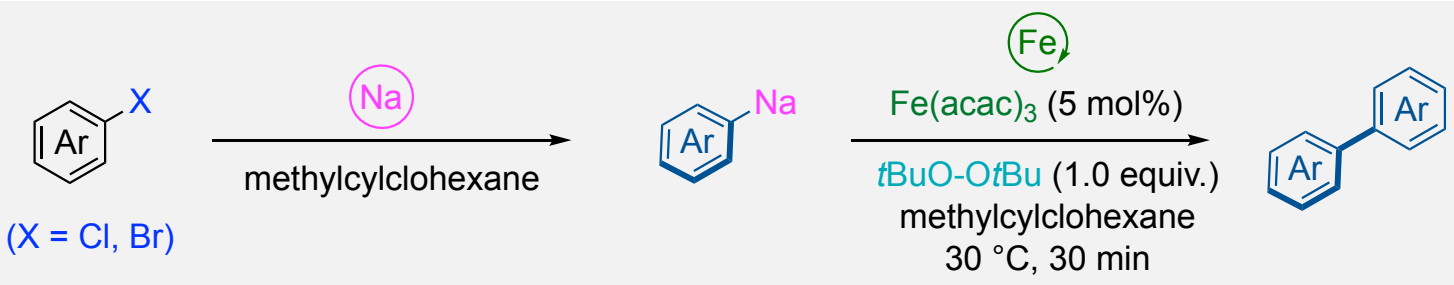


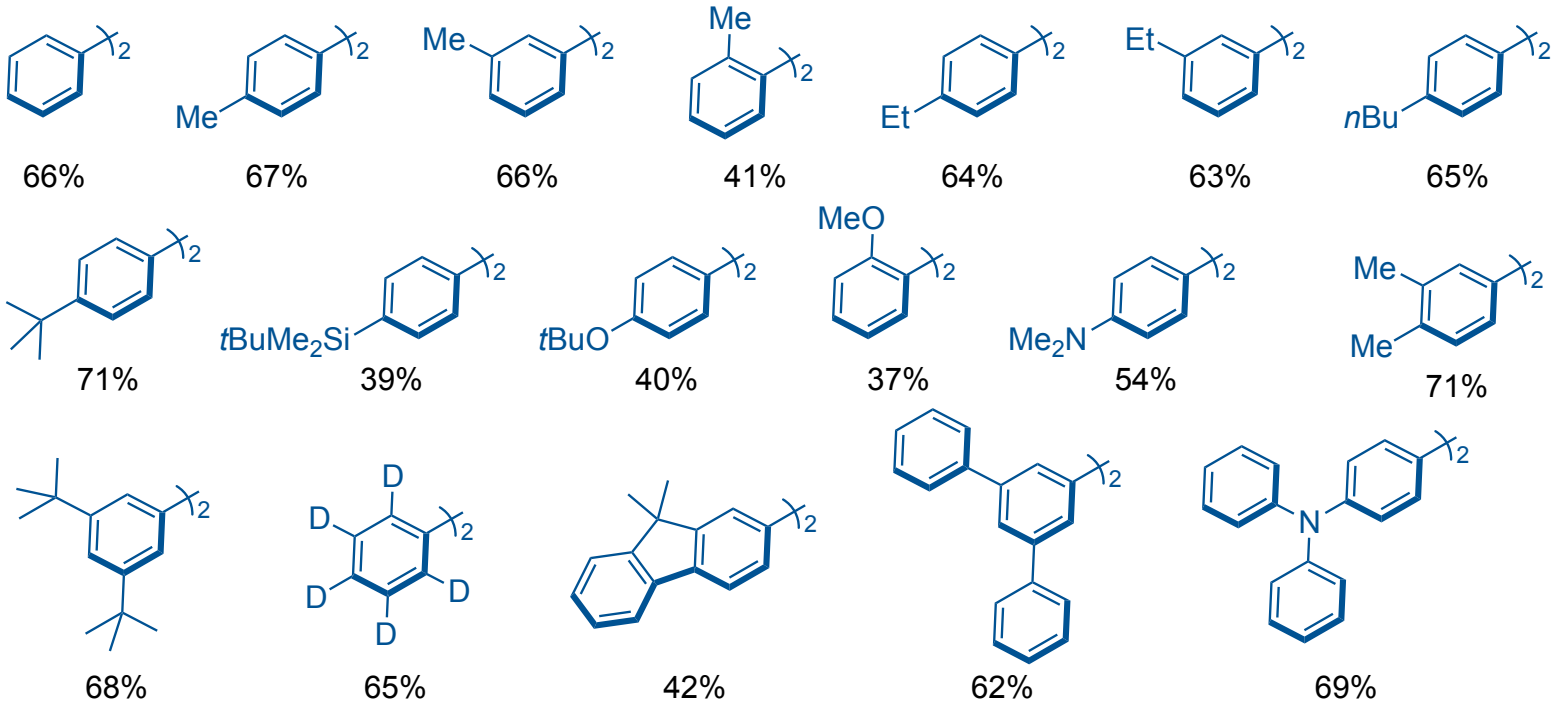
Asako et al, *Nat. Cat.* **2019**, *2*, 297



FeX_n	Cosolvent	Yield (%)
$FeCl_2$	C_6H_6	1
$FeBr_2$	C_6H_6	5
$Fe(acac)_2$	C_6H_6	52
$Fe(acac)_3$	**C_6H_6**	**74**
$Fe(acac)_3$	THF	36

Making Organosodium Chemistry Even More Sustainable



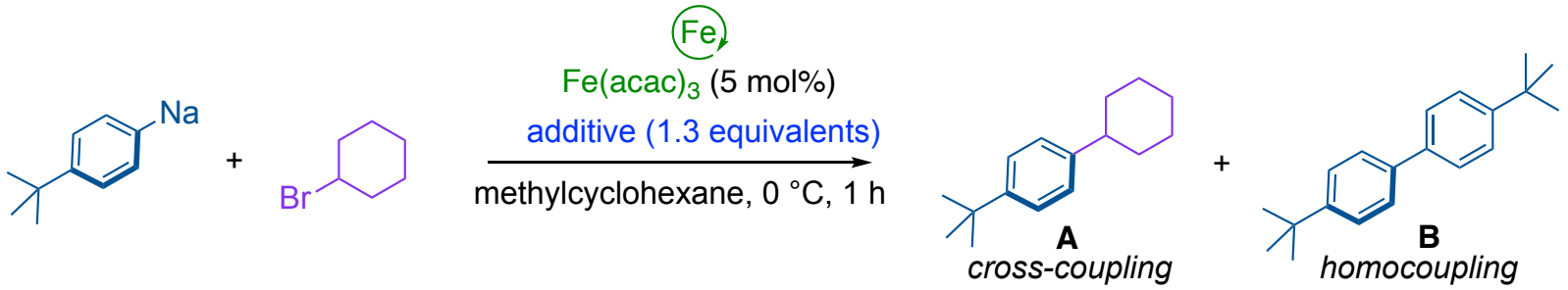


Nat. Synth. **2025**, 10.1038/s44160-025-00771-1

Fe-catalysed Cross-coupling of Organosodium Reagents

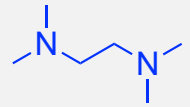
UNIVERSITÄT BERN

Assessing cross-coupling reactivity



Catalyst	Yield A (%)	Yield B (%)
$Fe(acac)_3$	**83**	**12**
none	0	3
$Pd(acac)_2$	0	10
$Ni(acac)_2$	0	30
$Cu(acac)_2$	0	4

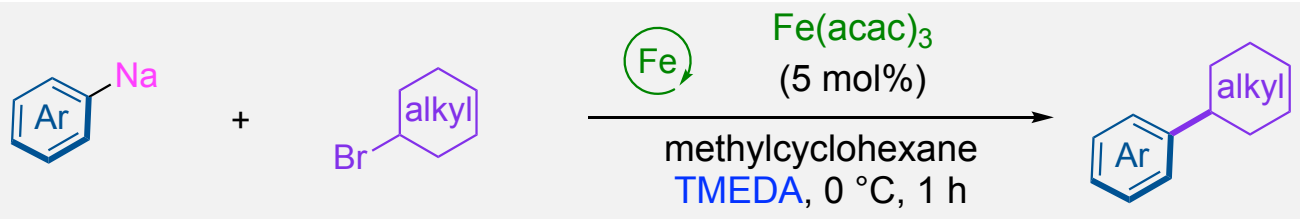
additive	Yield (%) (A:B ratio)
none	9 (30:70)
THF	29 (45:55)
15-crown-5	6 (11:89)
TMEDA	54 (76:24)
TMEDA (10 eq)	**96 (87:13)**

TMEDA = 

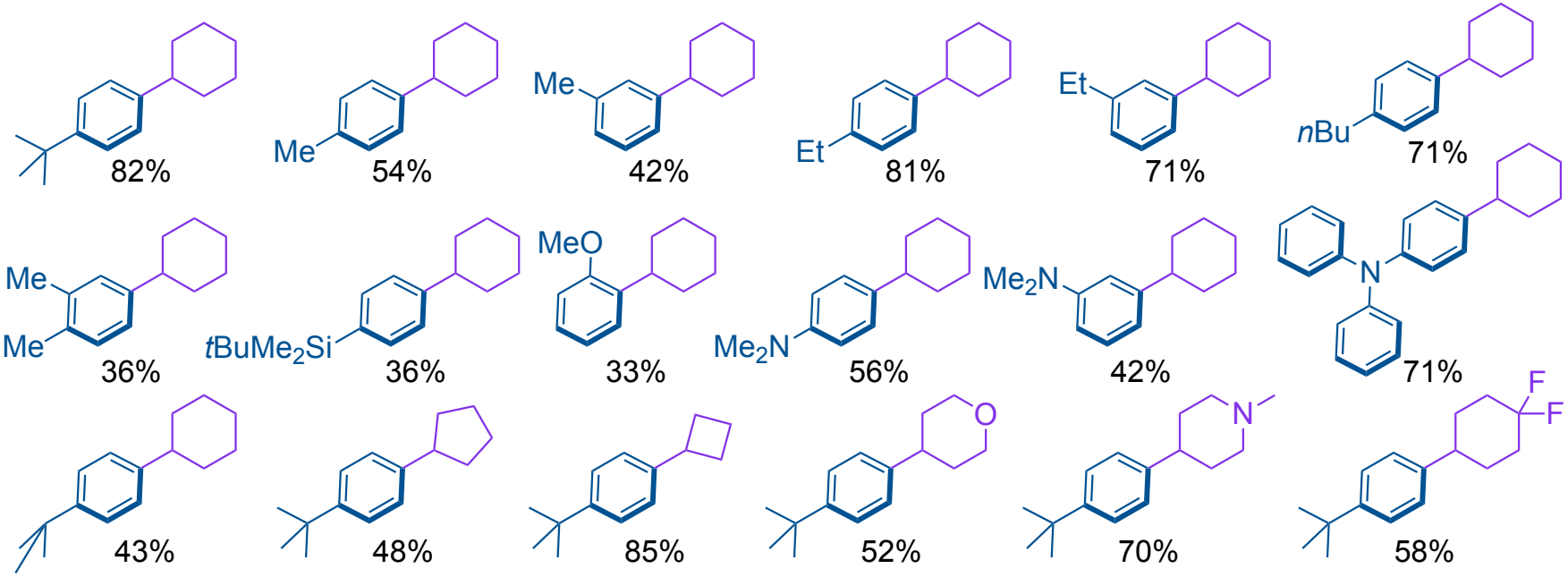
Fe is key to promote the C-C bond forming process

Nat. Synth. **2025**, 10.1038/s44160-025-00771-1

Fe-catalysed Cross-coupling of Organosodium Reagents



25 examples
Mild reaction conditions
No external ligands



Nat. Synth. **2025**, 10.1038/s44160-025-00771-1

Fe-catalysed Cross-coupling of Organosodium Reagents

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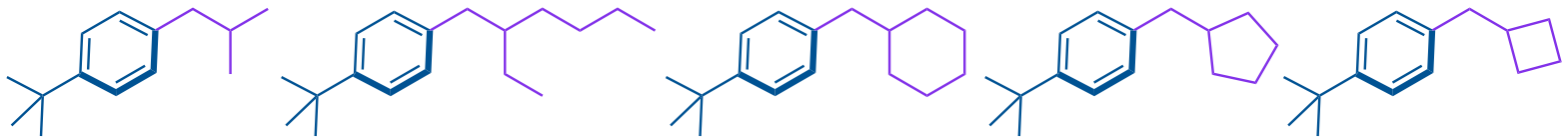
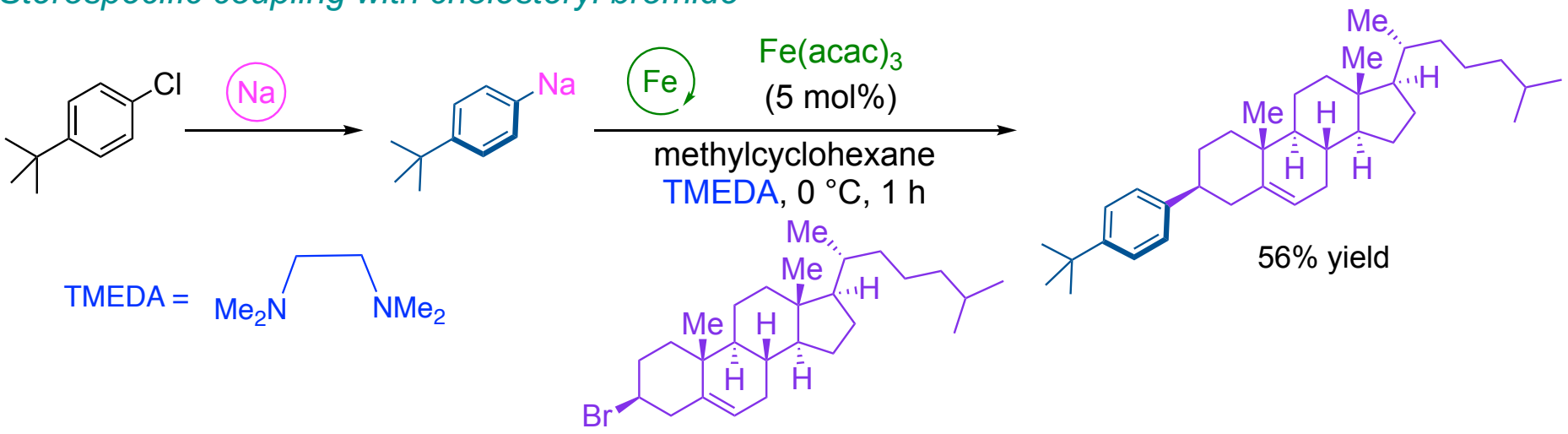
Scope using primary alkyl bromides



Sterospecific coupling with cholesteryl bromide



Nat. Synth. **2025**, 10.1038/s44160-025-00771-1

Fe-catalysed Cross-coupling of Organosodium Reagents

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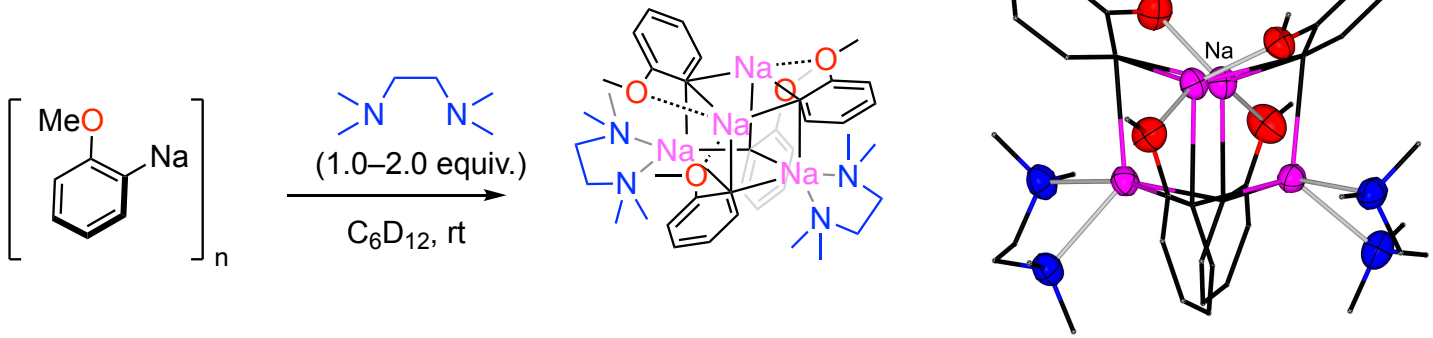
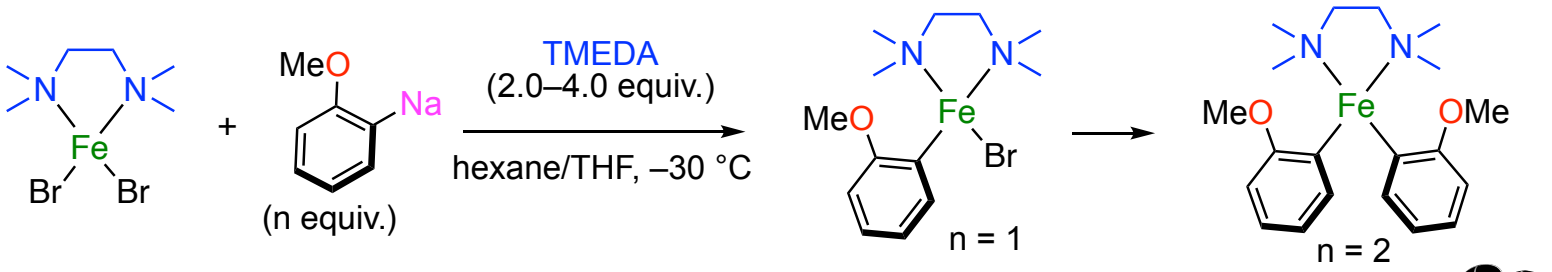
Understanding the role of TMEDA



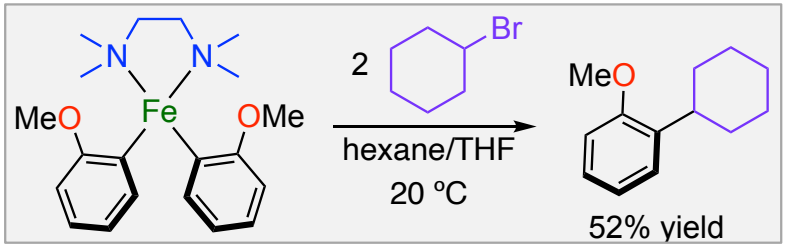
deaggreagation and activation of NaAr

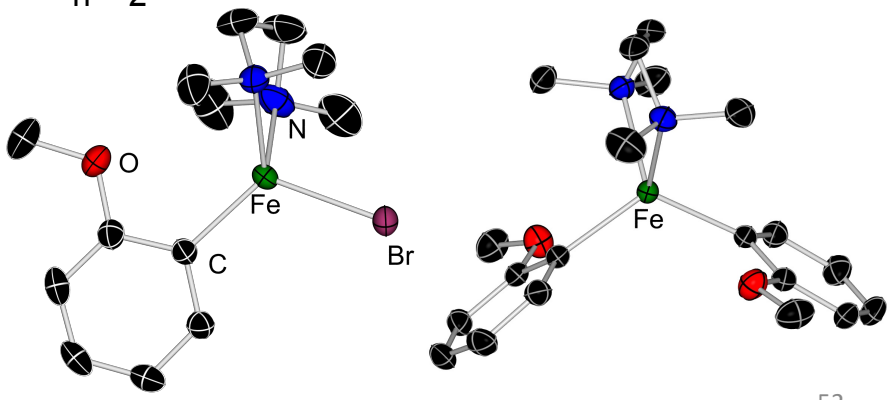


Coordinative stabilisation of Fe(II) center



Andreu Tortajada

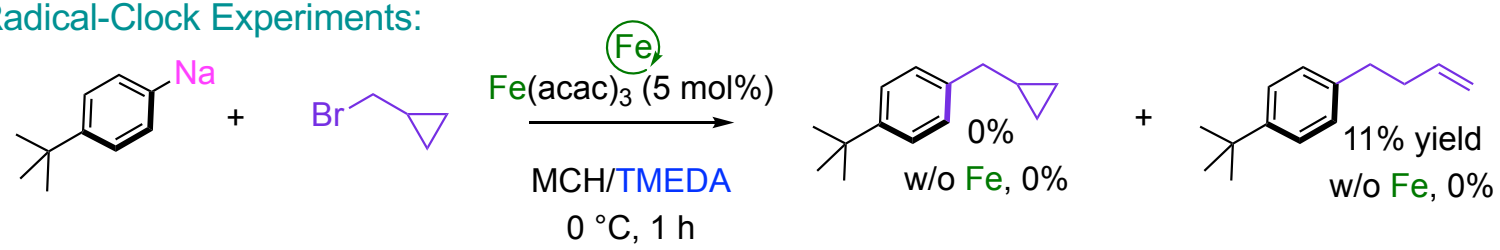




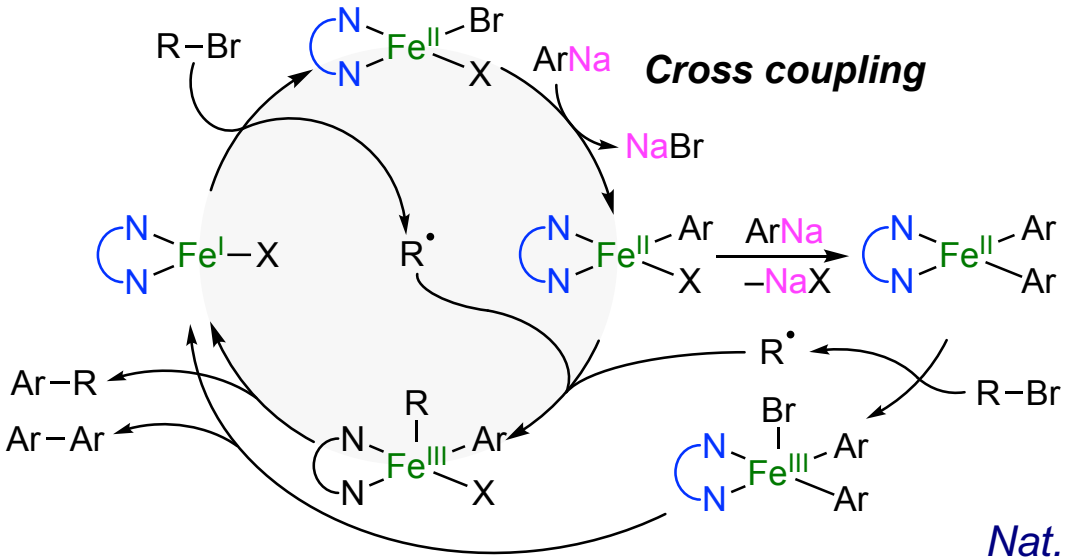
Nat. Synth. **2025**, 10.1038/s44160-025-00771-1

Fe-catalysed Cross-coupling of Organosodium Reagents

Radical-Clock Experiments:



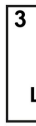
Consistent with alkyl radical formation



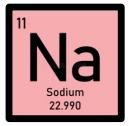
M. Neidig, *Angew. Chem. Int. Ed.* **2022**, *61*, e202114986:
Fe cataysed cross-coupling of ArMgX

Nat. Synth. **2025**, 10.1038/s44160-025-00771-1

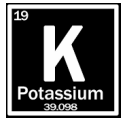
Harnessing Organopotassium Reagents for Cross-coupling Applications



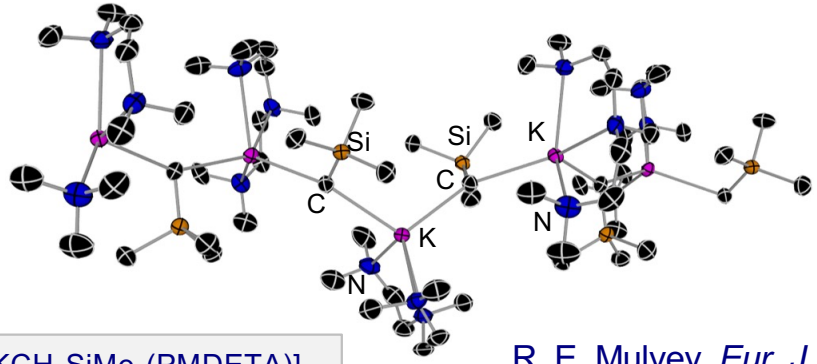
Abundance: 0.002 %
Electronegativity: 0.98
Size: 145 pm



Abundance: 2.6 %
Electronegativity: 0.93
Size: 180 pm



Abundance: 2.4 %
Electronegativity: 0.82
Size: 235 pm



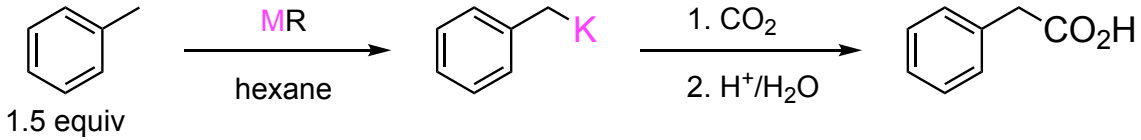
$[KCH_2SiMe_3(PMDETA)]_n$

Organopotassium Reagents

- highly aggregated structures
- limited solubility in hydrocarbons
- untamed reactivity
- no applications in cross-coupling reactions

R. E. Mulvey, *Eur. J. Inorg. Chem.* **2011**, 721

Assessing ability of organopotassium reagents for C-H metalation



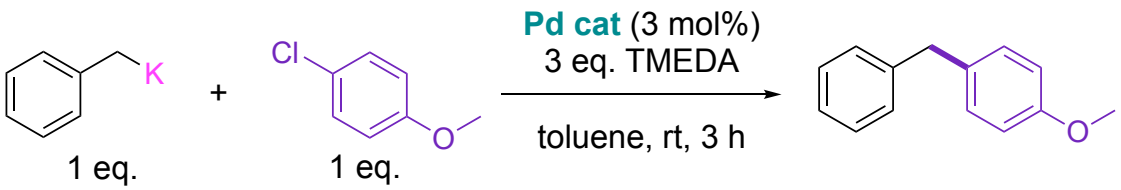
KR is drastically superior as a base!

MR	Yield (%)
KCH_2SiMe_3	**80**
*n*BuLi + K*O*t*Bu*	65
$LiCH_2SiMe_3$	0
$NaCH_2SiMe_3$	5



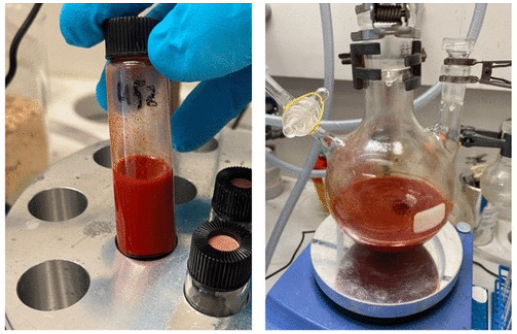
KCH_2Ph generated *in situ in hexane*

Harnessing Organopotassium Reagents for Cross-coupling Applications



1 eq. 1 eq.

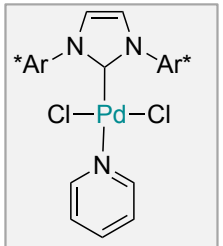
Pd cat	Yield (%)
none	5
Pd(P*t*Bu$_3$)$_2$	4



one pot approach:
$LiCH_2SiMe_3$ / KO*t*Bu
multigram synthesis:
85% yield (7 mmol scale)

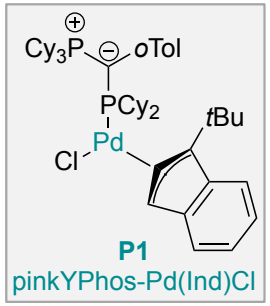
Pd(P*t*Bu$_3$)$_2$

cross couplings of **Li**Ar with **ArBr**:
Feringa et al, *Nat. Chem.* **2013**, *5*, 667



Pd-PEPPSI-IPent

cross couplings of **Na**Ar with **ArBr**:
Asako et al, *Nat. Cat.* **2019**, *2*, 297



P1
pinkYPhos-Pd(Ind)Cl

cross couplings of **Li**Ar with **ArCl**:
Gessner et al, *Angew. Chem. Int. Ed.* **2020**, *59*, 20596

highly electron rich ylide phosphine



David Anderson



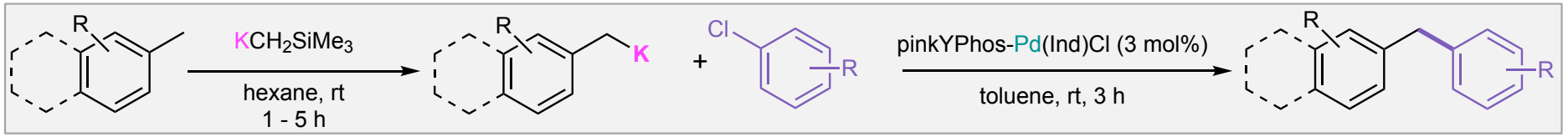
Daniel Knyszek

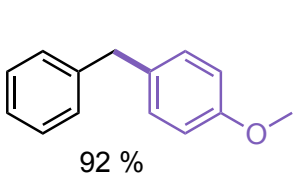


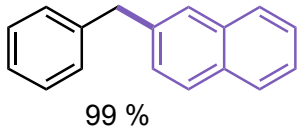
Viktoria Gessner

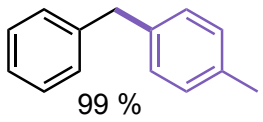
J. Am. Chem. Soc., **2025**, 147, 5417

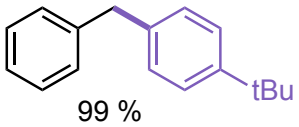
Harnessing Organopotassium Reagents for Cross-coupling Applications

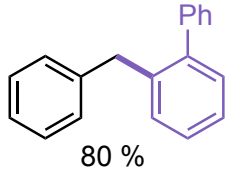


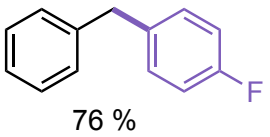


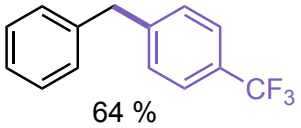


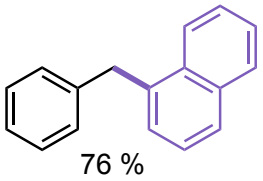


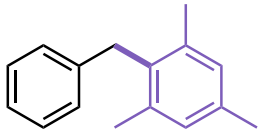


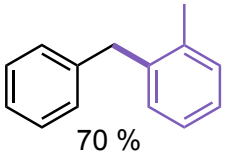




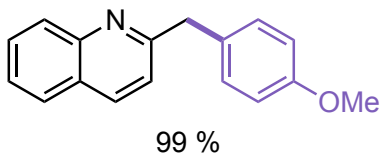


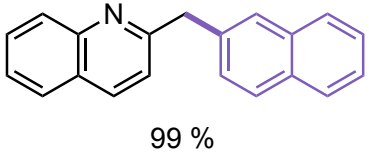


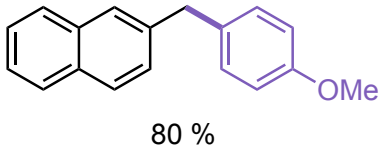


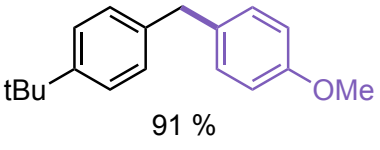


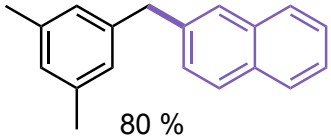
- direct metalation
- fast catalysis
- over 25 examples
- simple one-pot, RT approach

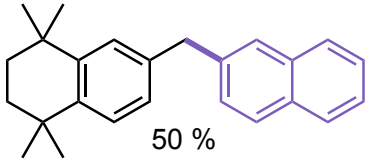


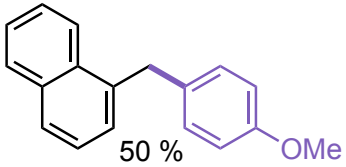


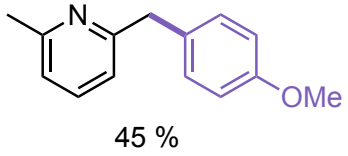


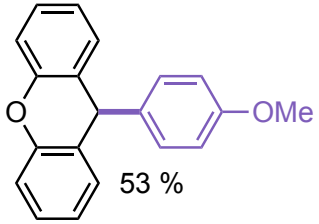


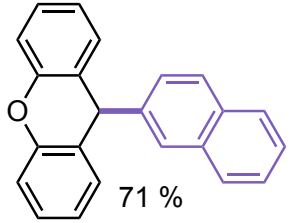






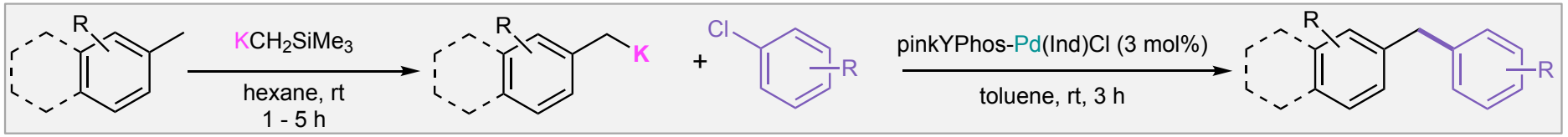




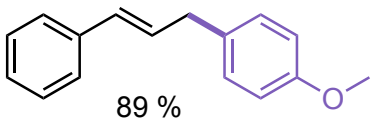


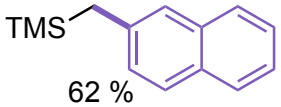
J. Am. Chem. Soc., **2025**, 147, 5417

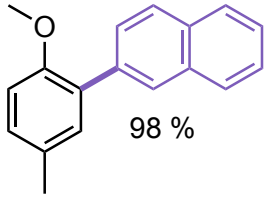
Harnessing Organopotassium Reagents for Cross-coupling Applications

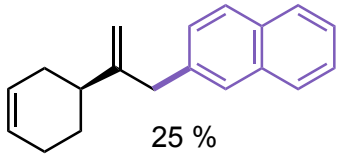


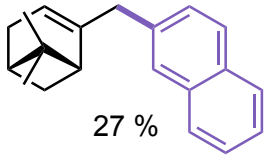
further potassium reagents

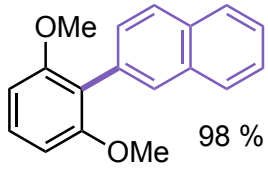


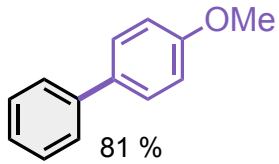












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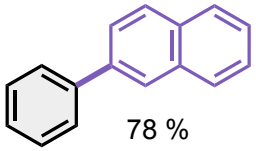
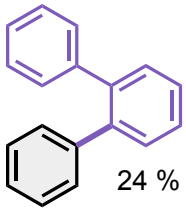
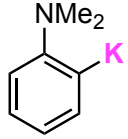
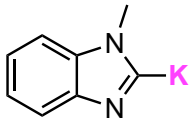




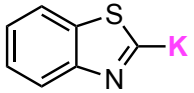
Limitations



7 % unselective cross-coupling



12 %, unselective cross-coupling



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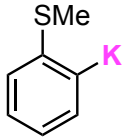

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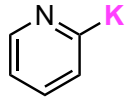

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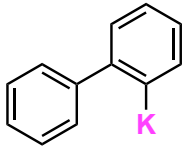
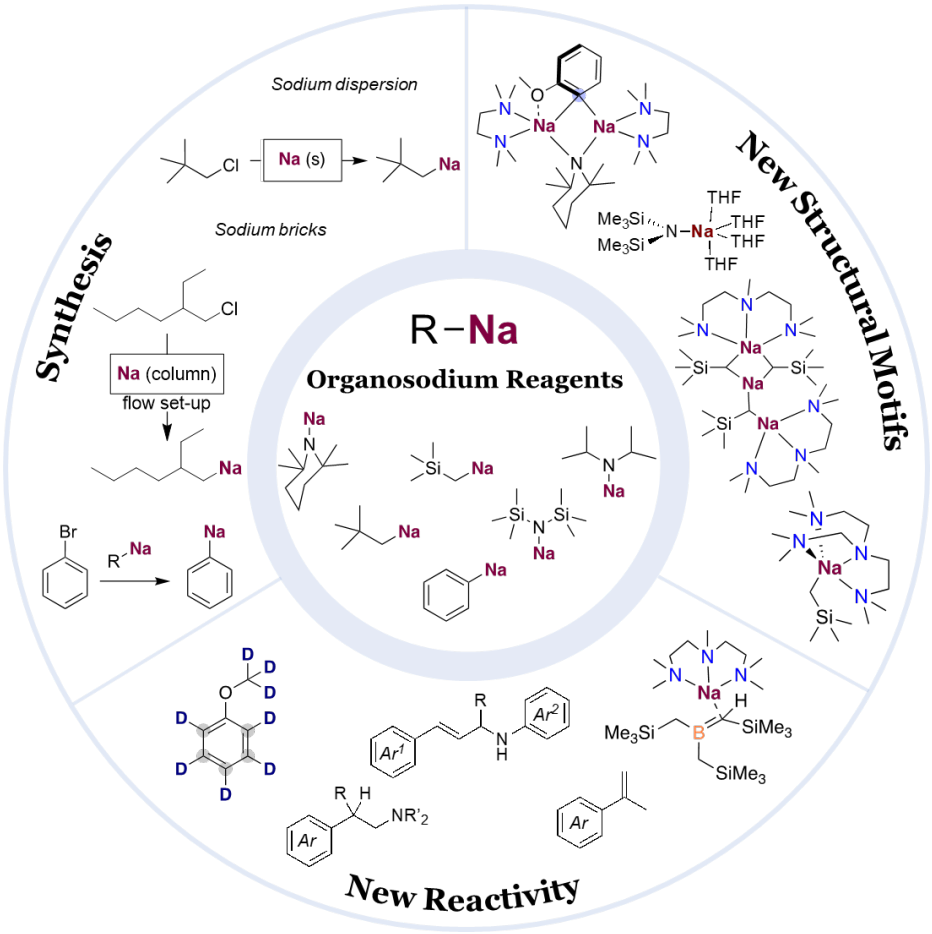
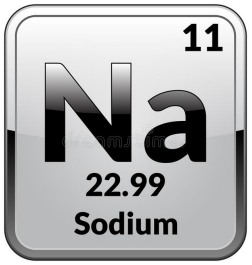


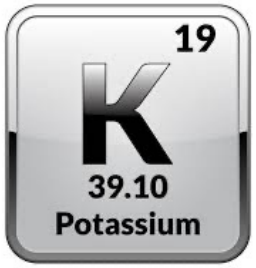
10 % unselective metallation

J. Am. Chem. Soc., **2025**, 147, 5417

Conclusions and Outlook



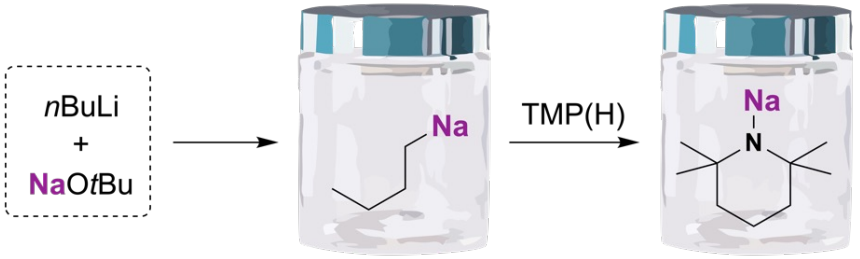




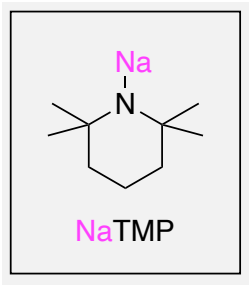
- ✓ power of Na and K to mediate metalation processes
- ✓ application in catalysis
- ✓ reactivity underpinned by **coordination effects** and **chemical cooperation**!

Angew. Chem. Int. Ed.,**2024**, 63, e202313556 (*Minireview*)

*n*BuNa and NaTMP: synthesis in a gram scale



Commercial reagents ▪ *Multi gram scale* ▪ *High purity*





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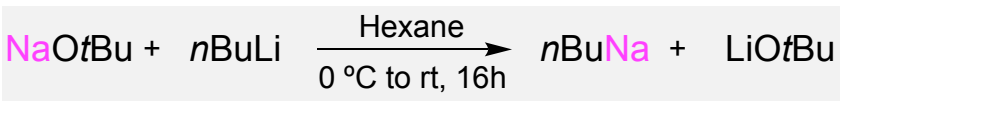

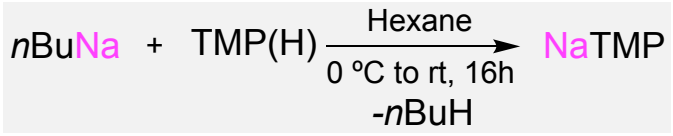

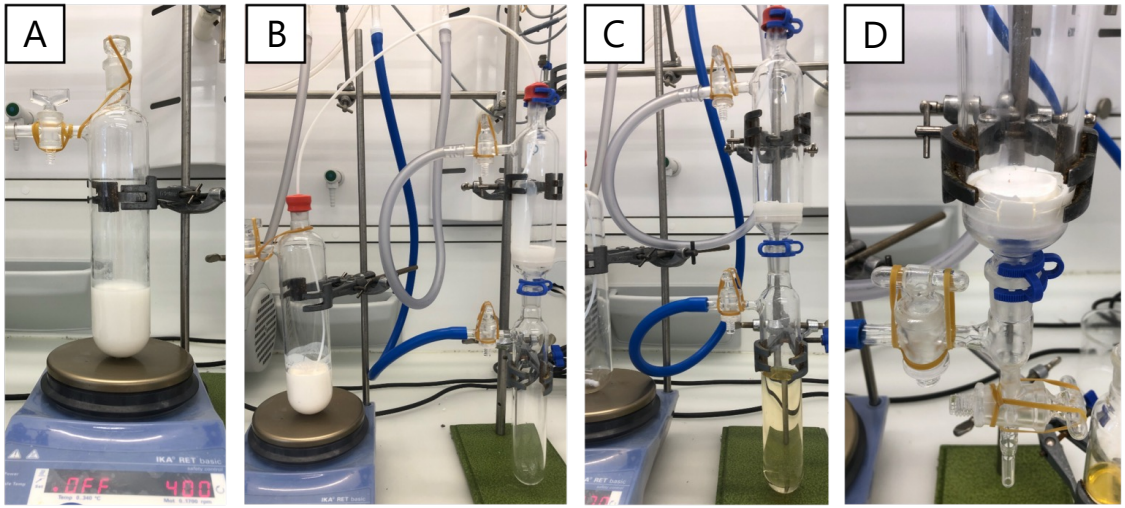

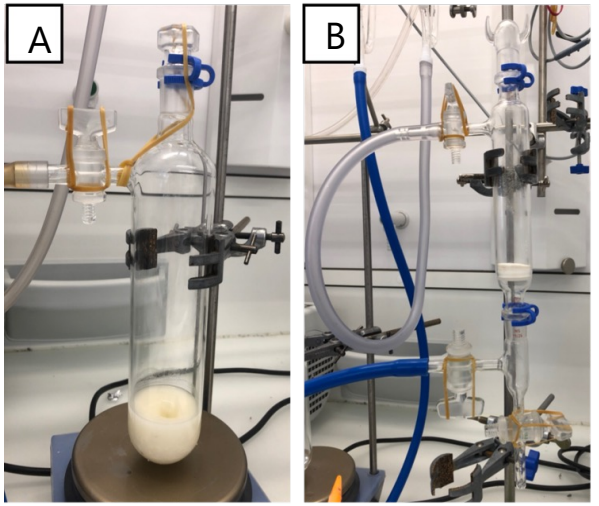

Helv. Chim. Acta **2022**, *105*, e202200060 (*open access*)

Acknowledgements

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Jennifer Kuziola
Luca Vedani
Na Jin
Jelena Krizic
Rafela Feuz
Zippora Brüllhardt
Ioannis Vagiakos
Talia Mathers
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