Nickel-catalyzed Suzuki-Miyaura coupling of amides

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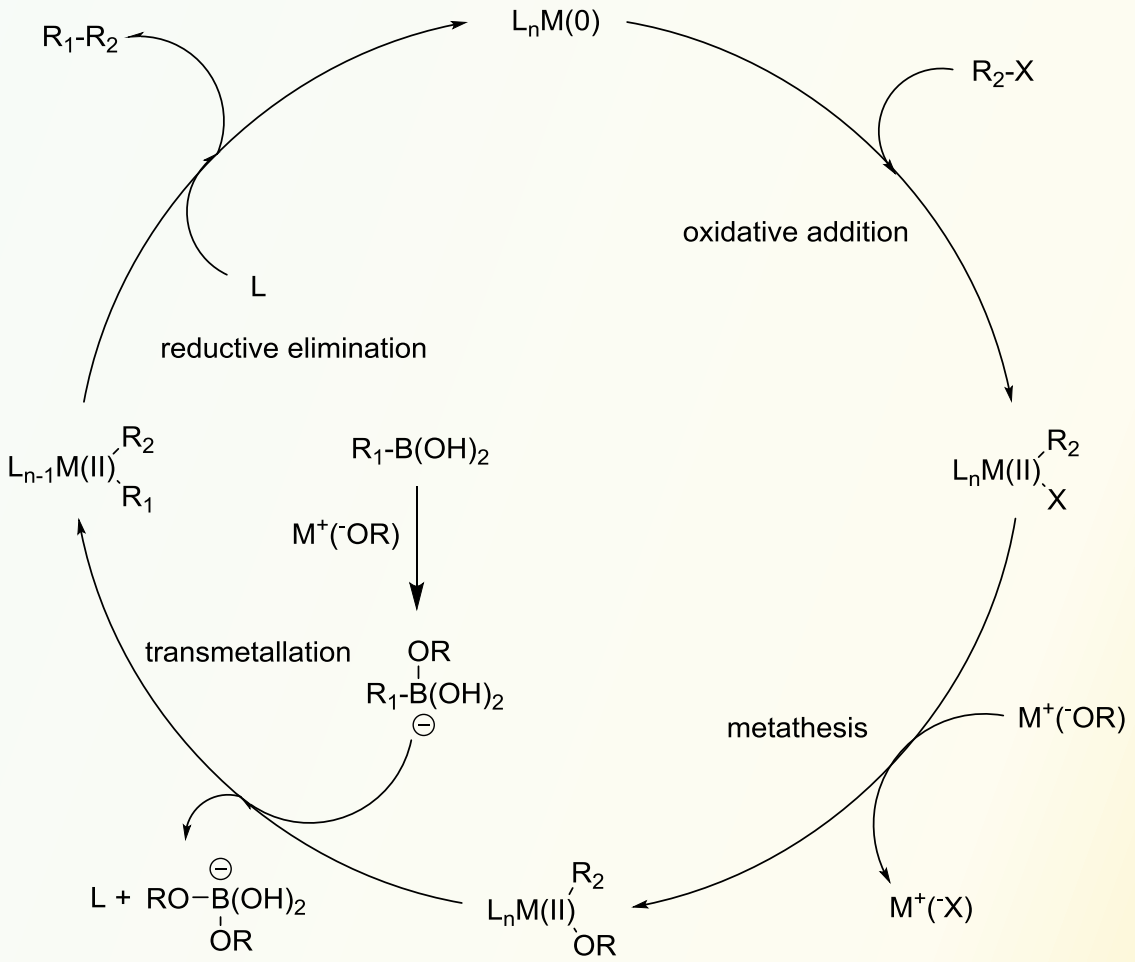
DOI: 10.1038/NCHEM.2388

Joseph Salamoun

Current Literature 11/21/15

Wipf Group

“Generalized” Suzuki-Miyaura Cross-Coupling Mechanism



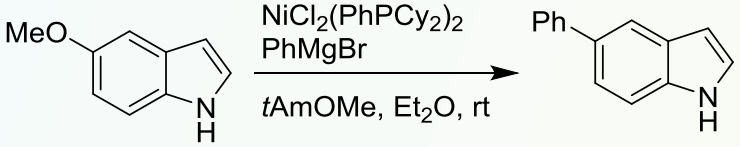
“The mechanism of the oxidative addition-transmetallation-reductive elimination process is very complex and the exact details depend on solvents, ligands, the transition metals, and additives.” – From *Transition Metals in the Synthesis of Complex Organic Molecules*, by Hegedus L. S. and Söderberg B. C. G., 3rd ed., 2010.

Ni vs. Pd

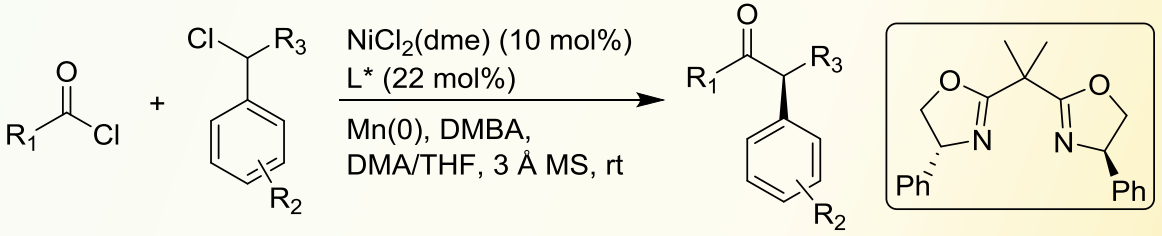
Nickel	Palladium
-1, **0**, **+1**, **+2**, **+3**, +4	**0**, +1, **+2**, +3, **+4**
Smaller atomic radius	Larger atomic radius
Less electronegative	More electronegative
Harder	Softer
Facile oxidative addition	Facile reductive elimination
Facile β-migratory insertion	Facile β-hydride elimination
Radical pathways more accessible	
Less expensive	

Review: *Nature* **2014**, *509*, 299.

Nickel catalysis: “If I had a nickel for every time …”

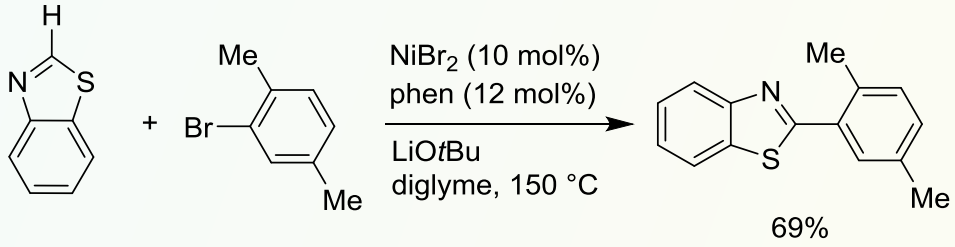


*t*Am = $CEtMe_2$

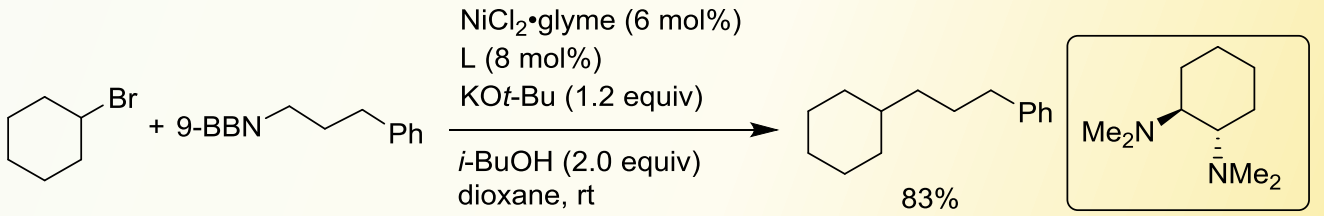


R_1, R_3 = alkyl

72-94% ee



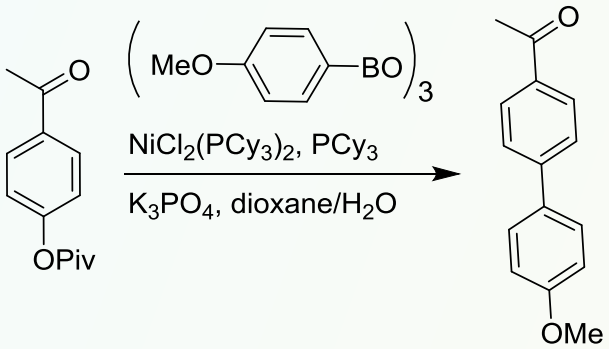
69%



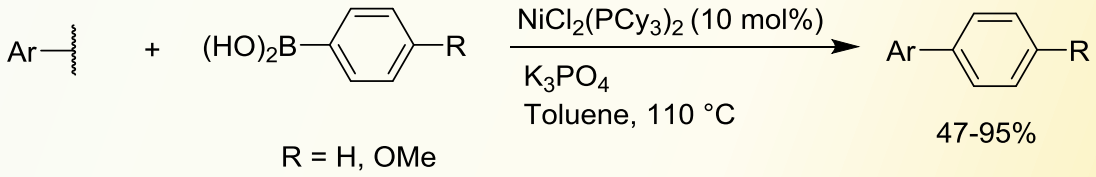
83%

Reviews: *Nature* **2014**, *509*, 299.
Eur. J. Org. Chem **2013**, 19.

Nickel catalysis: “If I had a nickel for every time …”

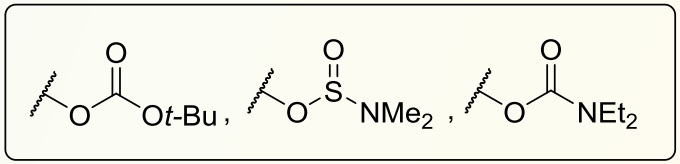


75%

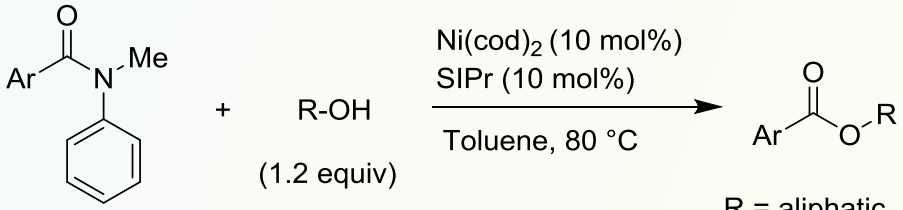


R = H, OMe

47-95%



From the Garg group:
J. Am. Chem. Soc. **2009**, 131, 17748.
J. Am. Chem. Soc. **2011**, 133, 6352.

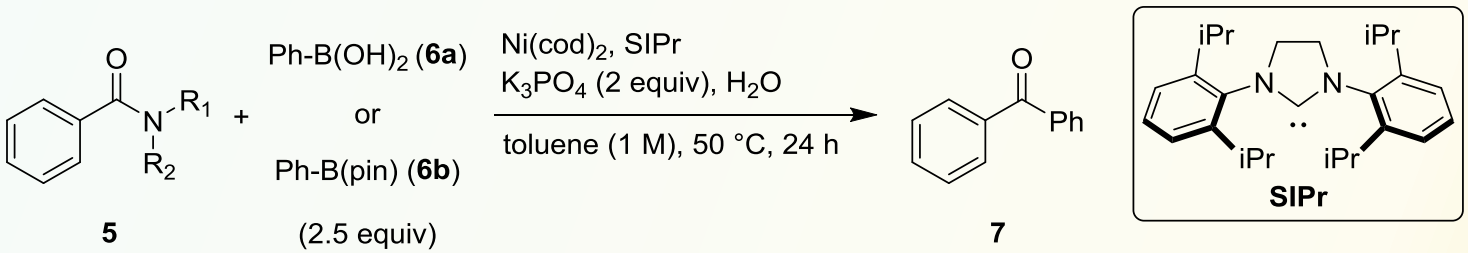


R = aliphatic
49-91%

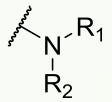
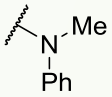
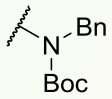
From the Garg group:
Nature **2015**, *524*, 79.

Reviews: *Nature* **2014**, *509*, 299.
Eur. J. Org. Chem **2013**, 19.

Screening of amide substitutions



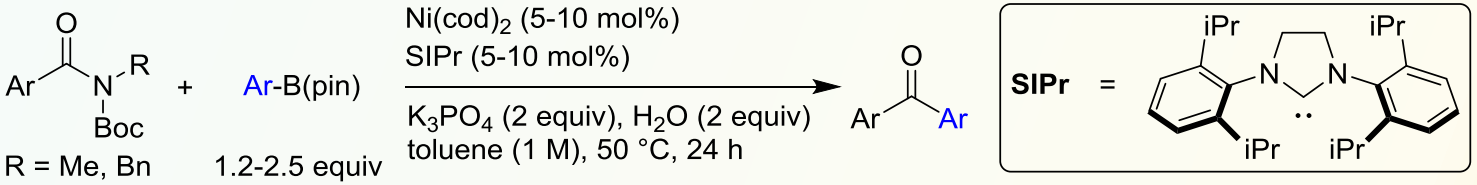
5 **7**

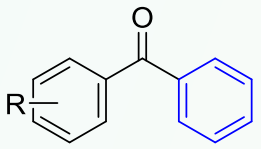
entry		boron source	$Ni(cod)_2$ (mol%)	SIPr (mol%)	H_2O (equiv)	Yield*
1	 **5a**	**6a**	10	10	-	12%
2	 **5b**	**6a**	10	10	-	42-89%
3	**5b**	**6b**	10	10	-	7%
4	**5b**	**6b**	10	10	2.0	>99%
5	**5b**	**6b**	5	5	2.0	>99%

- Yields determined by ^1H NMR.
- More details on screening in SI.

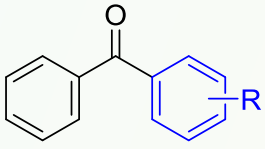
12/29/2015
DOI:10.1038/NCHEM.2388

Scope of cross-coupling of amides

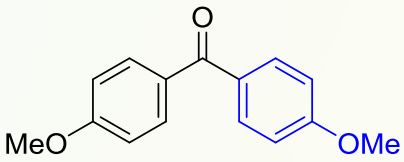




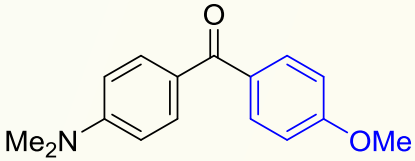
7, R = H, 96%
8, R = *p*-Me, 92%
9, R = *m*-Me, 91%
10, R = *o*-Me, 51%



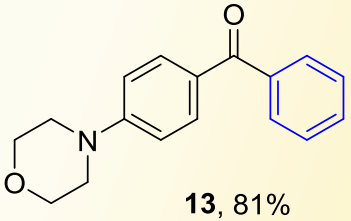
8, R = *p*-Me, 73%
9, R = *m*-Me, 80%
10, R = *o*-Me, 66%



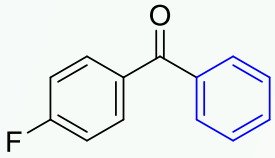
11, 78%



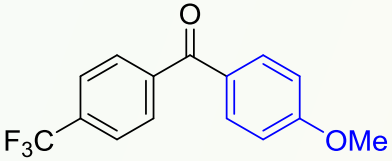
12, 59%



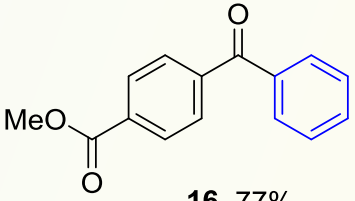
13, 81%



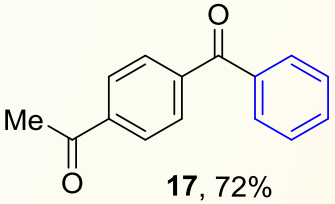
14, 90%



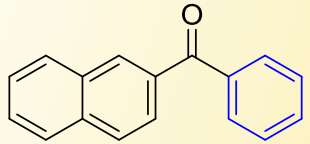
15, 85%



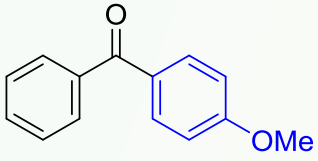
16, 77%



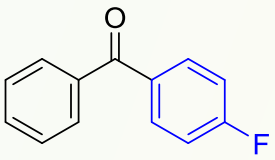
17, 72%



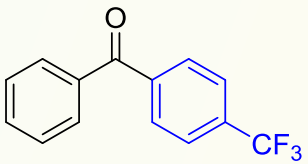
18, 70%



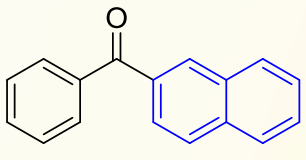
19, 95%



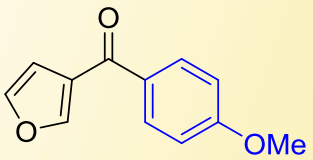
14, 88%



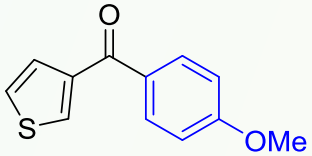
20, 81%



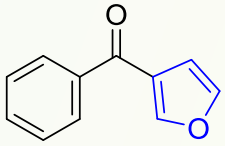
18, 94%



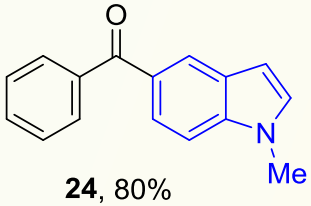
21, 64%



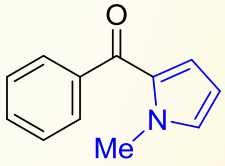
22, 66%



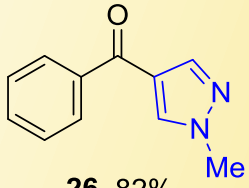
23, 86%



24, 80%



25, 96%

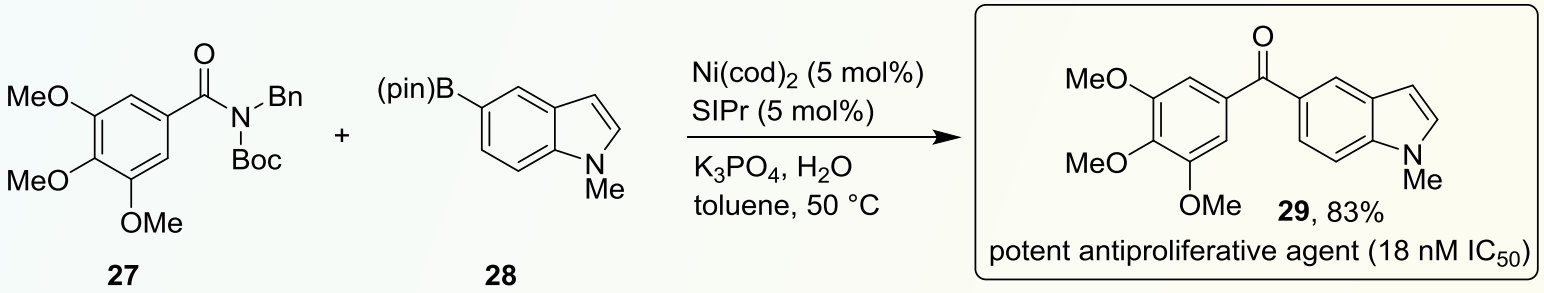


26, 82%

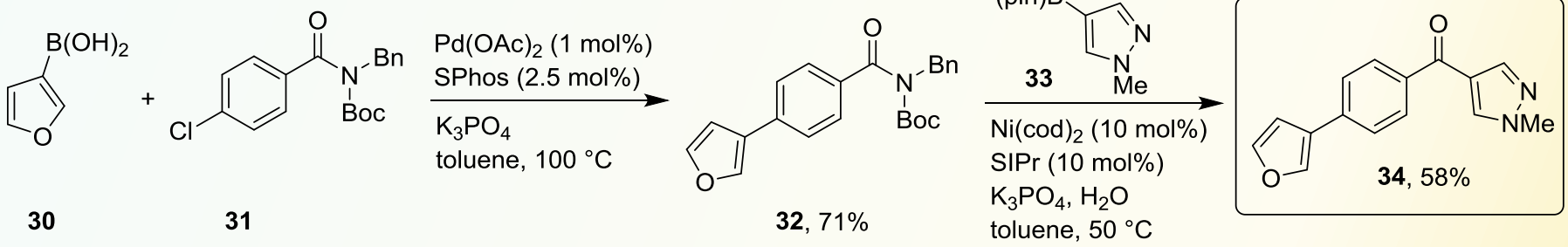
* Yields determined by ^{1}H NMR. Screening for functional group compatibility in SI.

DOI:10.1038/NCHEM.2388

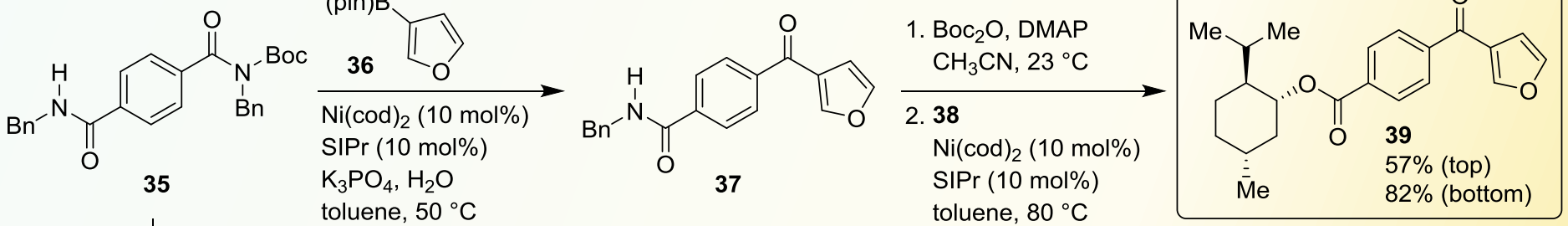
Applications of cross-coupling



27 **28**



30 **31**



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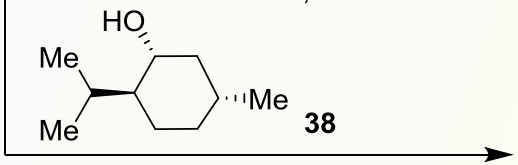
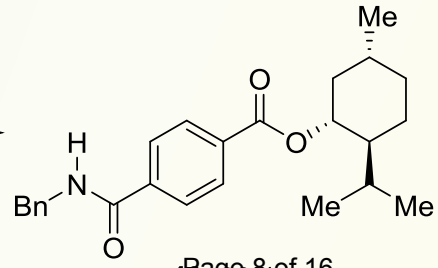
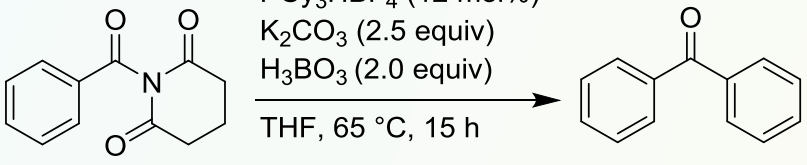




40, 90%

DOI:10.1038/NCHEM.2388

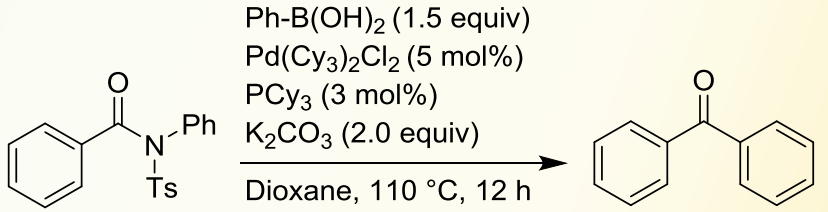
Some alternative methods for making diaryl ketones



95%

* Scope includes aliphatic amides.

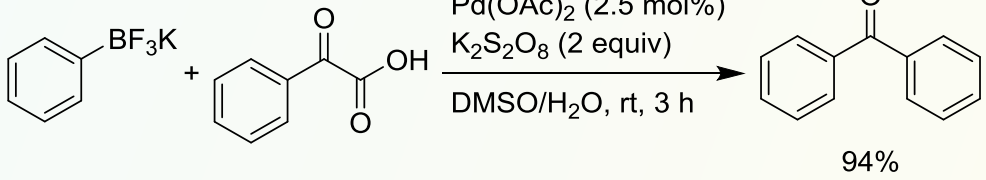
Org. Lett. **2015**, *17*, 4364.



94%

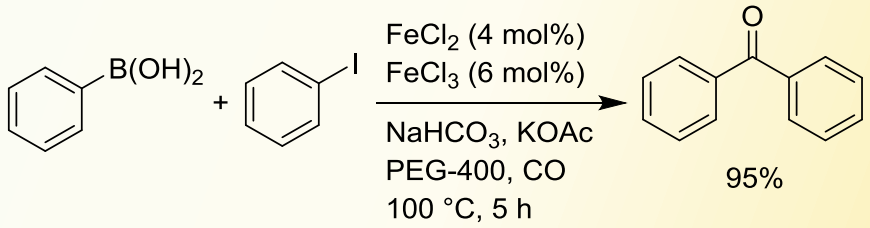
* Scope includes aliphatic amides.

Chem. Commun. **2015**, *51*, 5089.



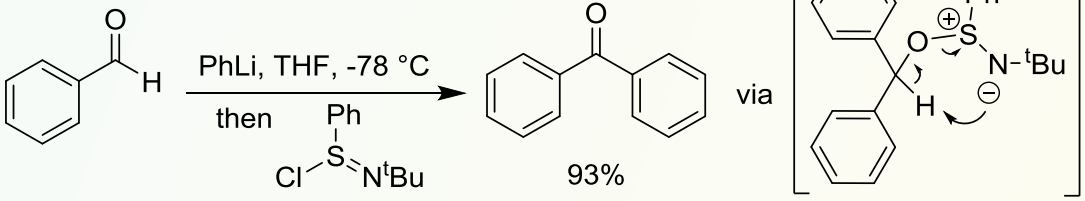
94%

Org. Lett. **2011**, *13*, 2062.



95%

Chem. Commun. **2014**, *50*, 3874.



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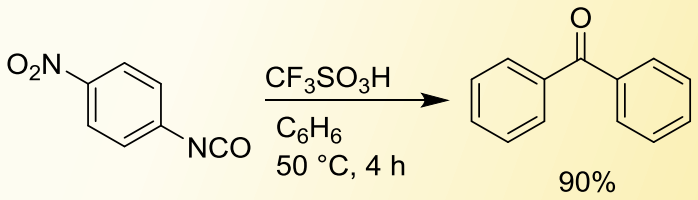


90%

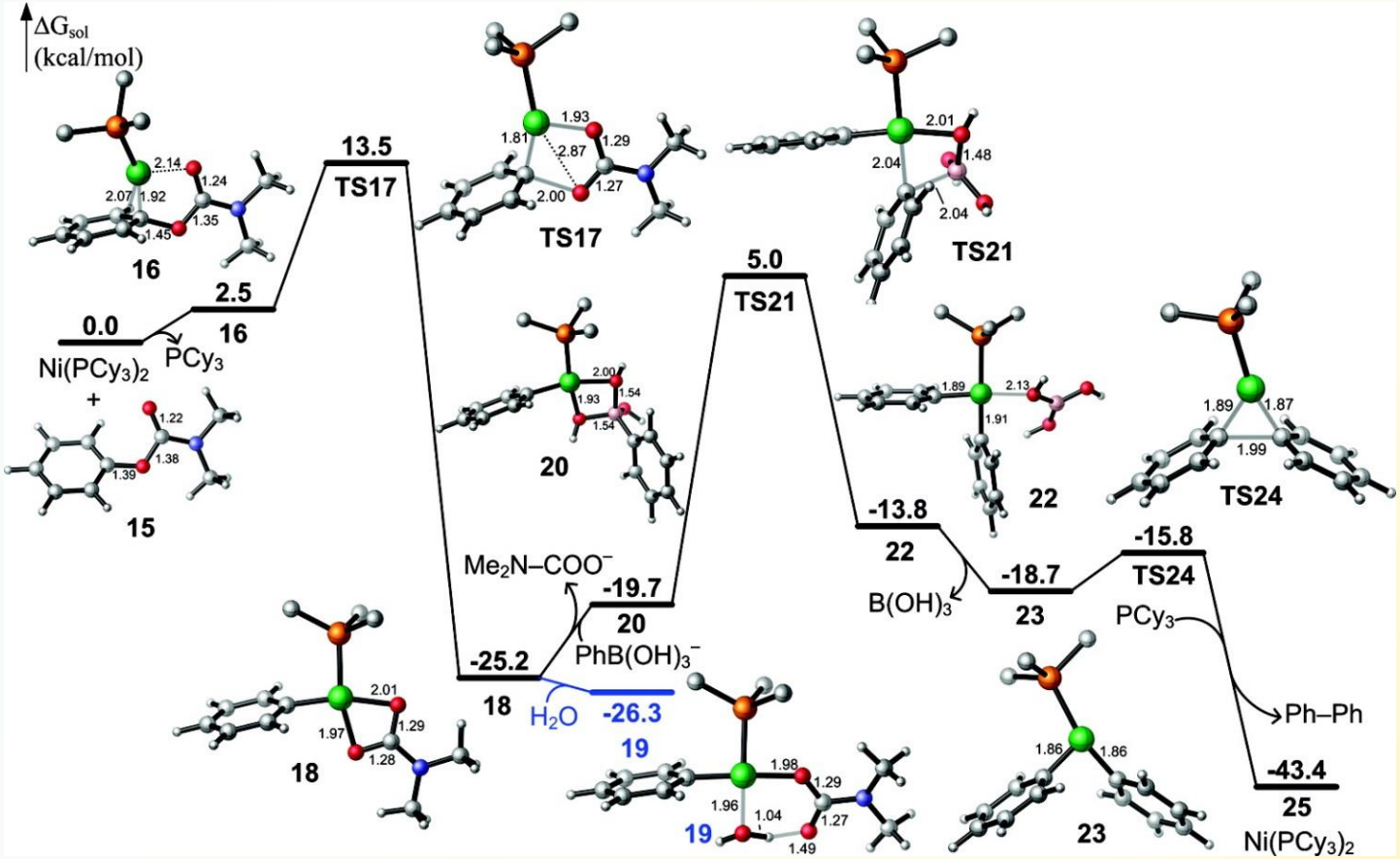
J. Org. Chem. **2012**, *77*, 5788.

Org. Lett. **2006**, *8*, 5073.

Conclusions

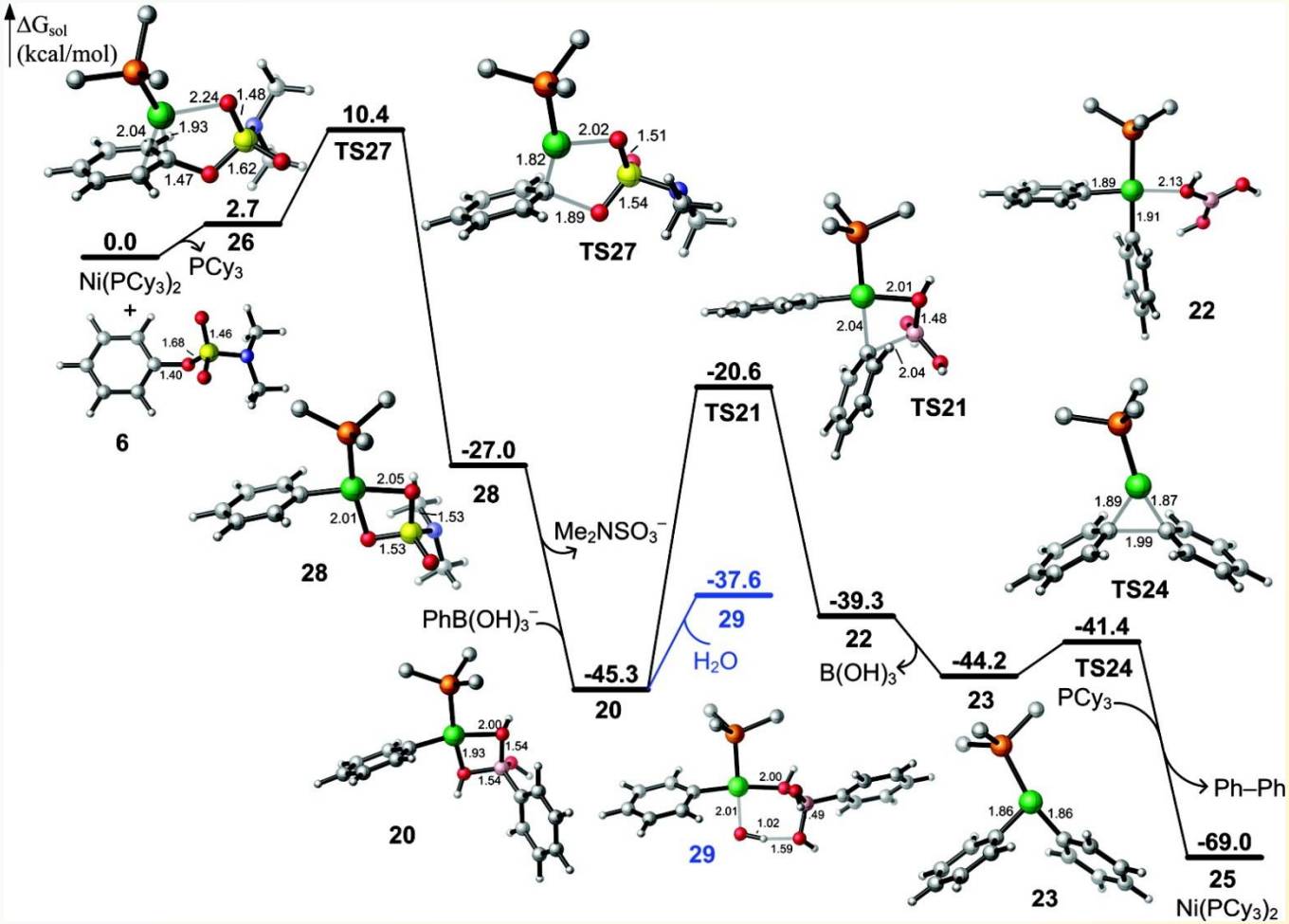
- New application of nickel catalysis with potential for great utility, especially in med chem.
- Amides are relatively stable and widely accessible.
- Very good yields (but by NMR and most purifications by prep TLC)
- Limited scope (only aromatic amides).
- Synthetic advantage over traditional acylations not clear.

- Future Outlook:
  - If the Garg group can demonstrate the coupling of aliphatic amides with chiral aliphatic boronic esters, then this methodology could have a major impact.



Gibbs free energy profile of Ni-catalyzed Suzuki−Miyaura cross-coupling reaction of phenyl *N*,*N*-dimethyl *O*-carbamate **15** with phenylboronic acid. PCy3 was used as ligand in the calculations. For clarity, the cyclohexyl groups on the ligand are not shown.

Published in: Kyle W. Quasdorf; Aurora Antoft-Finch; Peng Liu; Amanda L. Silberstein; Anna Komaromi; Tom Blackburn; Stephen D. Ramgren; K. N. Houk; Victor Snieckus; Neil K. Garg; *J. Am. Chem. Soc.* **2011,** 133, 6352-6363.
DOI: 10.1021/ja200398c



Gibbs free energy profile of the Ni-catalyzed Suzuki−Miyaura cross-coupling reaction of *N*,*N*-dimethyl phenyl *O*-sulfamate with phenylboronic acid. PCy3 was used as ligand in the calculations. For clarity, the cyclohexyl groups on the ligand are not shown.

Published in: Kyle W. Quasdorf; Aurora Antoft-Finch; Peng Liu; Amanda L. Silberstein; Anna Komaromi; Tom Blackburn; Stephen D. Ramgren; K. N. Houk; Victor Snieckus; Neil K. Garg; *J. Am. Chem. Soc.* **2011,** 133, 6352-6363.
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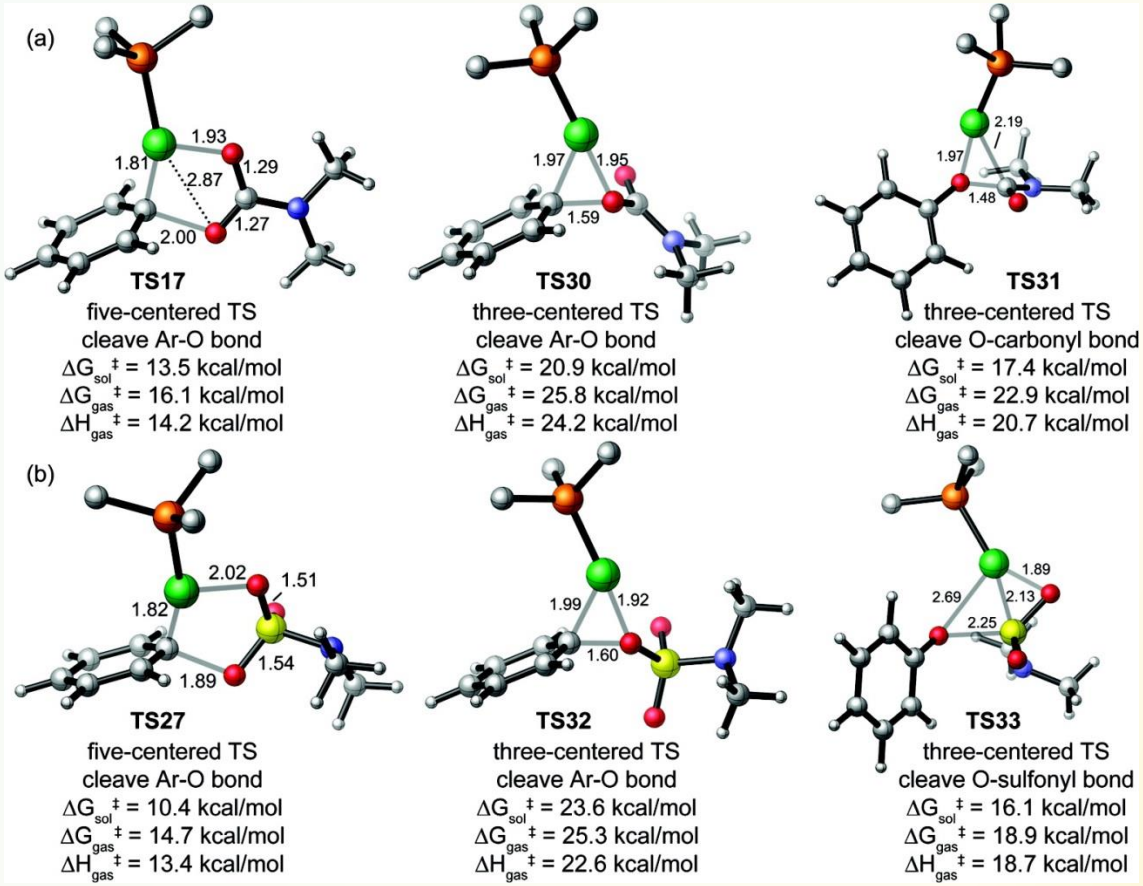
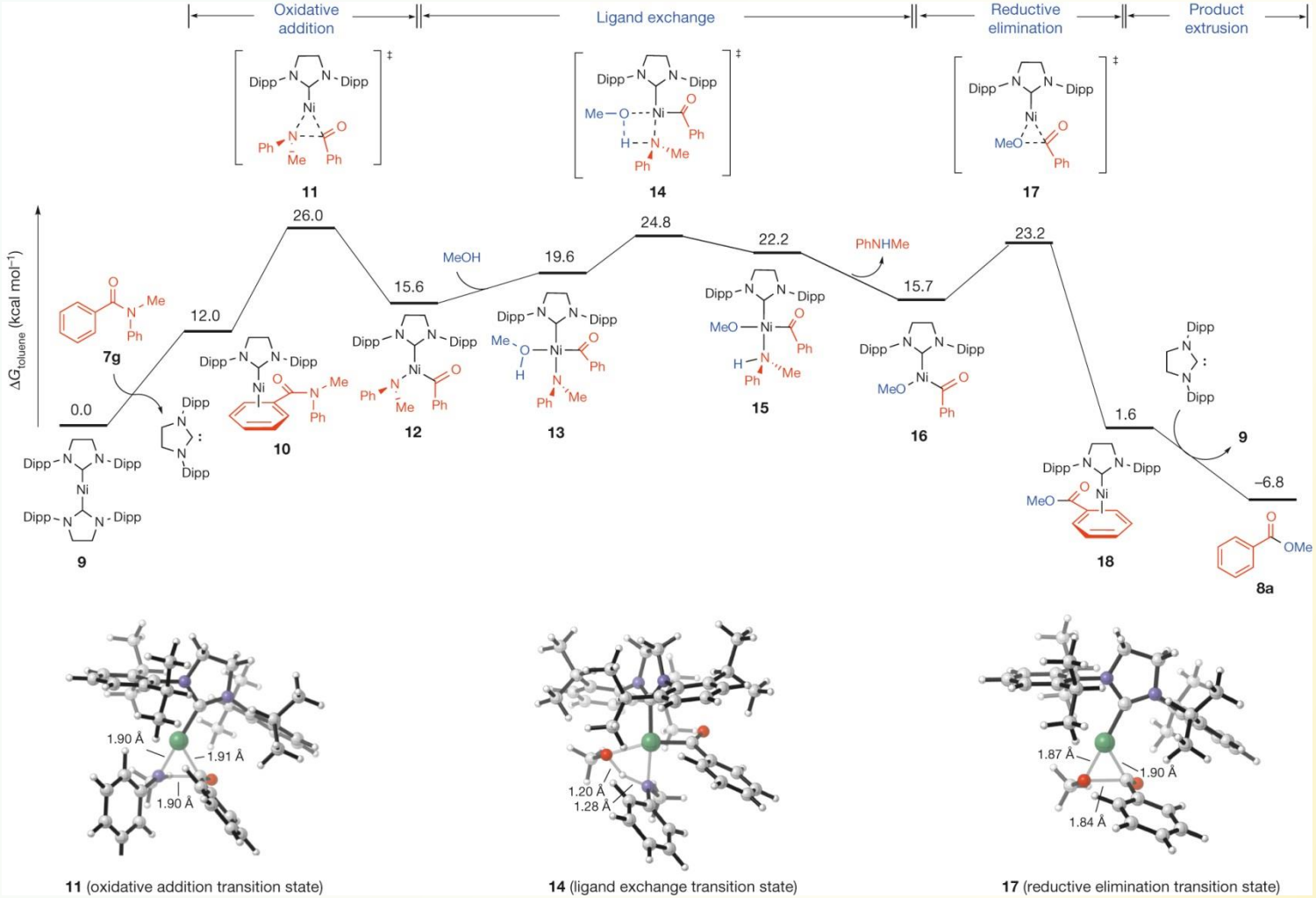


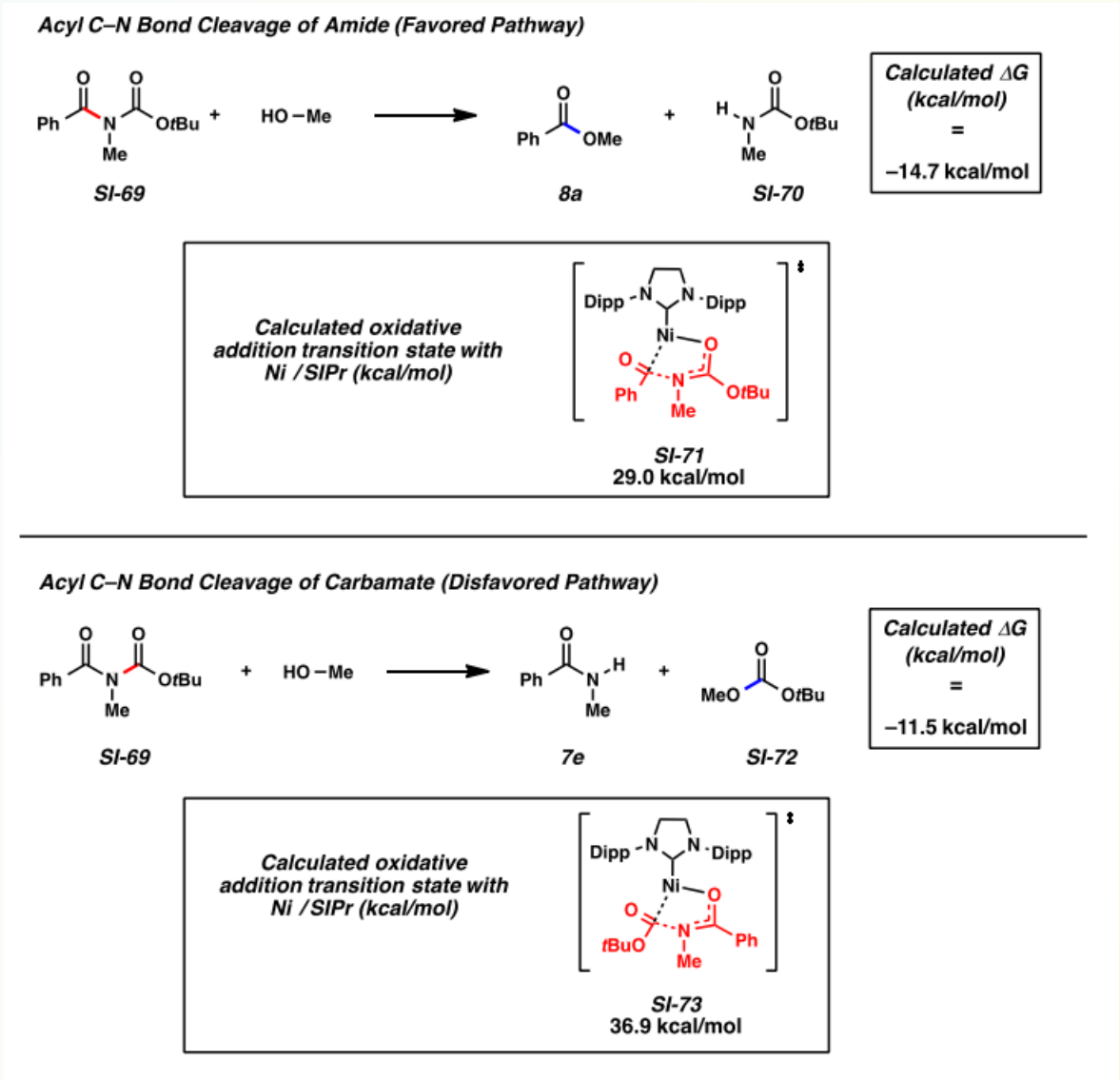
Transition-state structures of Ni-catalyzed oxidative additions of (a) *N*,*N*-dimethyl phenyl *O*-carbamate and (b) *N*,*N*-dimethyl phenyl *O*-sulfamate. PCy3 was used as ligand in the calculations. For clarity, the cyclohexyl groups on the ligand are not shown.

Published in: Kyle W. Quasdorf; Aurora Antoft-Finch; Peng Liu; Amanda L. Silberstein; Anna Komaromi; Tom Blackburn; Stephen D. Ramgren; K. N. Houk; Victor Snieckus; Neil K. Garg; *J. Am. Chem. Soc.* **2011,** 133, 6352-6363.
DOI: 10.1021/ja200398c

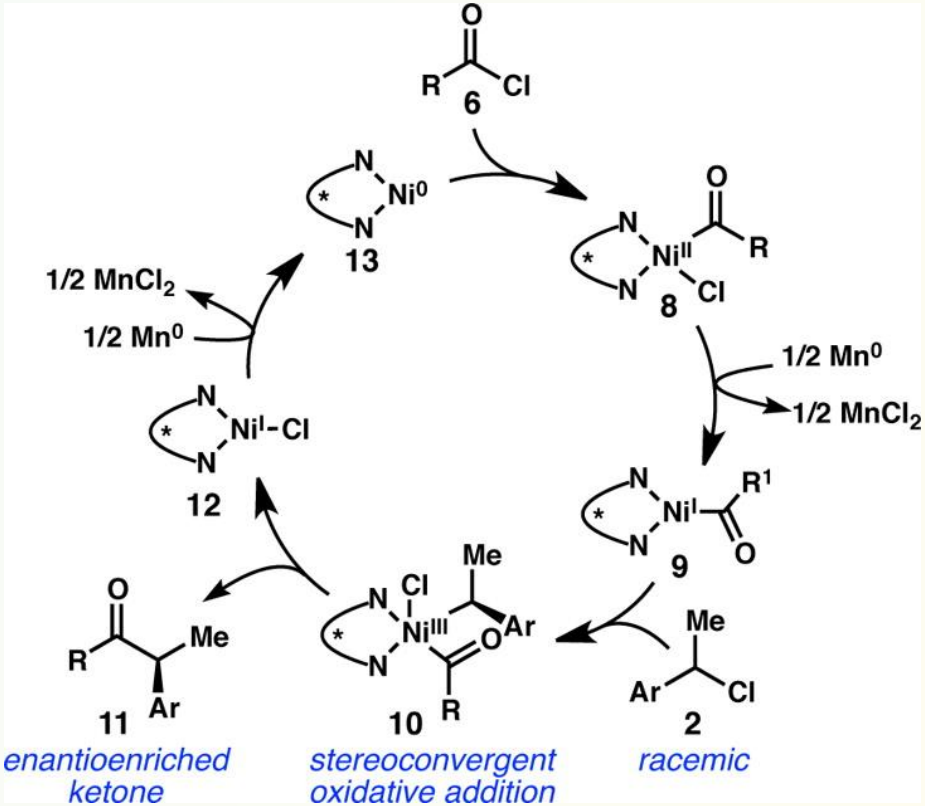
Computational study of catalytic cycle.



L Hie *et al. Nature 524*, 79-83 (2015) doi:10.1038/nature14615



In the SI of L Hie *et al. Nature 524*, 79-83 (2015) doi:10.1038/nature14615



Possible catalytic cycle.

Published in: Alan H. Cherney; Nathaniel T. Kadunce; Sarah E. Reisman; *J. Am. Chem. Soc.* **2013,** 135, 7442-7445.
DOI: 10.1021/ja402922w