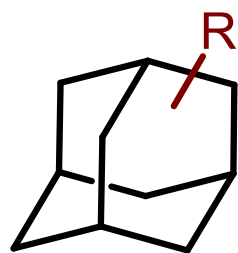


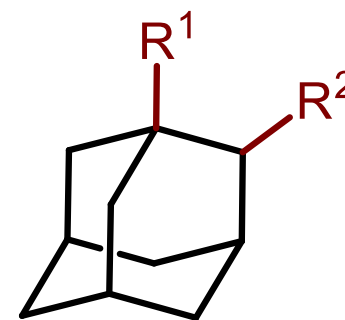
Classics in the synthesis of 1,2-disubstituted adamantane derivatives

Radim Hrdina

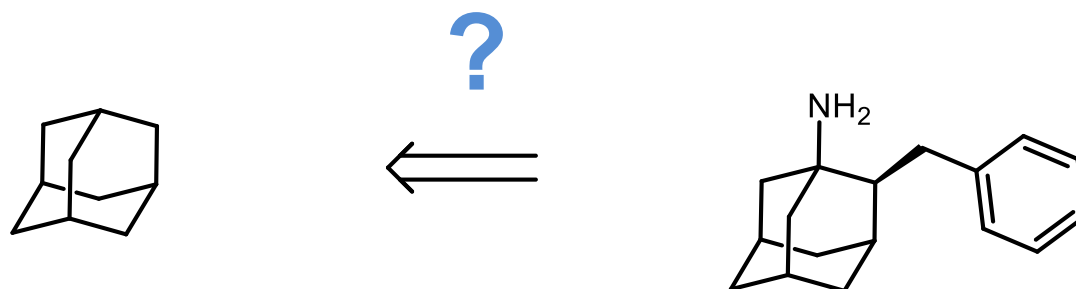
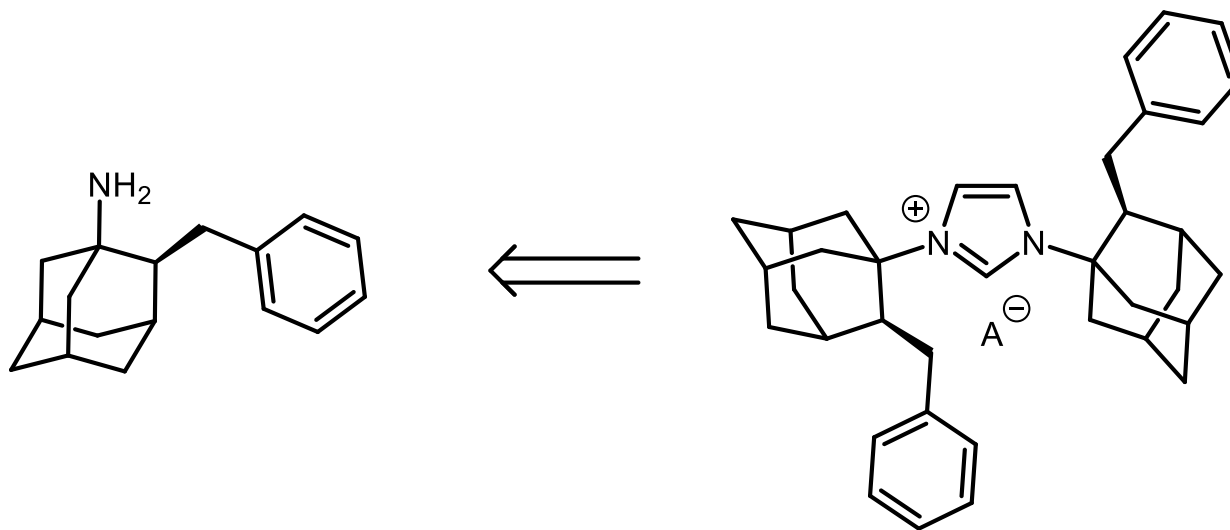
AG Schreiner
Seminar 31.8.2018



overview



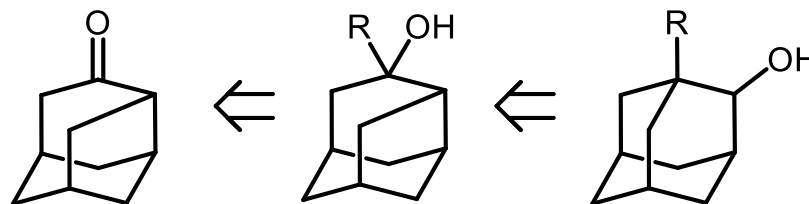
Are there still synthetic challenges?



Synthetic approaches to 1,2-disubstituted adamantane derivatives

1. Through the construction of the adamantane framework
 - 1.1 Protoadamantane route
 - 1.2 Noradamantane route
 - 1.3 Bicycloalkane route
 - 1.4 Total synthesis
 - 1.5 Diamondoids (separately presented)
2. Through the directed C–H functionalization of the adamantane framework
 - 2.1 Insertion reactions of electrophilic organic species
 - 2.2 Hydrogen radical abstraction reactions
 - 2.3 Carbometalations (C–H activation with transition metals)
 - 2.4 Hydride shift

Construction of the adamantane framework: protoadamantane



Wang, X. F.; Dong, Y. X.; Ezell, E. L.; Garrison, J. C.; Wood, J. K.; Hagen, J. P.; Vennerstrom, J. L. *Tetrahedron* **2017**, *73*, 2972.

Cindro, N.; Antol, I.; Mlinaric-Majerski, K.; Halasz, I.; Wan, P.; Basaric, N. *Journal of Organic Chemistry* **2015**, *80*, 12420.

Zoidis, G.; Sandoval, A.; Pineda-Farias, J. B.; Granados-Soto, V.; Felix, R. *Bioorganic & Medicinal Chemistry* **2014**, *22*, 1797.

Zoidis, G.; Kolocouris, N.; Kelly, J. M.; Prathalingam, S. R.; Naesens, L.; De Clercq, E. *European Journal of Medicinal Chemistry* **2010**, *45*, 5022.

Zoidis, G.; Tsotinis, A.; Kolocouris, N.; Kelly, J. M.; Prathalingam, S. R.; Naesens, L.; De Clercq, E. *Organic & Biomolecular Chemistry* **2008**, *6*, 3177.

Papanastasiou, I.; Tsotinis, A.; Kolocouris, N.; Prathalingam, S. R.; Kelly, J. M. *Journal of Medicinal Chemistry* **2008**, *51*, 1496.

Mlinaric-Majerski, K.; Kragol, G.; Ramljak, T. S. *Synlett* **2008**, 405.

Kolocouris, N.; Zoidis, G.; Fytas, C. *Synlett* **2007**, 1063.

Okazaki, T.; Ogawa, K.; Kitagawa, T.; Takeuchi, K. *Journal of Organic Chemistry* **2002**, *67*, 5981.

Abdelsayed, A. N.; Bauer, L. *Tetrahedron* **1988**, *44*, 1873.

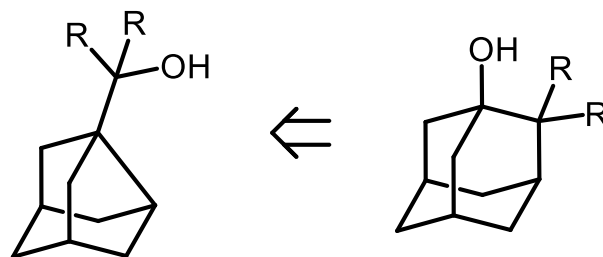
Chakrabarti, J. K.; Hotten, T. M.; Rackham, D. M.; Tupper, D. E. *Journal of the Chemical Society-Perkin Transactions 1* **1976**, 1893.

Tabushi, I.; Aoyama, Y. *Journal of Organic Chemistry* **1973**, *38*, 3447.

Lenoir, D.; Glaser, R.; Mison, P.; Schleyer, P. v. R. *Journal of Organic Chemistry* **1971**, *36*, 1821.

Cuddy, B. D.; Grant, D.; McKervey, M. A. *Journal of the Chemical Society C-Organic* **1971**, 3173.

Construction of the adamantane framework: noradamantane



Torres, E.; Fernandez, R.; Miquet, S.; Font-Bardia, M.; Vanderlinden, E.; Naesens, L.; Vazquez, S. *ACS Medicinal Chemistry Letters* **2012**, 3, 1065.

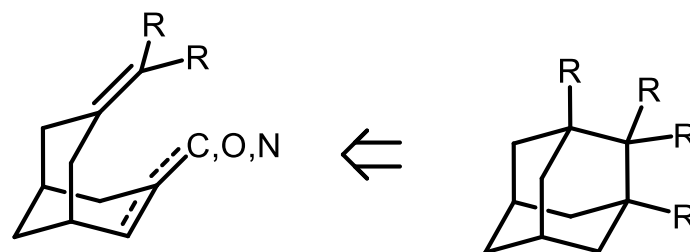
Moss, R. A.; Sauers, R. R.; Sheridan, R. S.; Tian, J. Z.; Zuev, P. S. *Journal of the American Chemical Society* **2004**, 126, 10196.

Stoelting, D. T.; Shiner, V. J. *Journal of the American Chemical Society* **1993**, 115, 1695.

Ohga, Y.; Takeuchi, K. *Journal of Physical Organic Chemistry* **1993**, 6, 293.

Sosnowski, J. J.; Rheingold, A. L.; Murray, R. K. *Journal of Organic Chemistry* **1985**, 50, 3788.

Construction of the adamantane framework: bicycloalkane



Kuga, T.; Sasano, Y.; Tomizawa, M.; Shibuya, M.; Iwabuchi, Y. *Synthesis* **2018**, *50*, 1820.

Ponomarenko, M. V.; Serguchev, Y. A.; Hirschberg, M. E.; Roschenthaler, G. V.; Fokin, A. A. *Chemistry-a European Journal* **2014**, *20*, 10383.

Serguchev, Y. A.; Ponomarenko, M. V.; Lourie, L. F.; Fokin, A. A. *Journal of Physical Organic Chemistry* **2011**, *24*, 407.

Denmark, S. E.; Lee, W. S., *Chemistry-an Asian Journal* **2008**, *3*, 327.

Serguchev, Y. A.; Ponomarenko, M. V.; Lourie, L. F.; Chernega, A. N. *Journal of Fluorine Chemistry* **2003**, *123*, 207.

Skomorokhov, M. Y.; Klimochkin, Y. N. *Russian Journal of General Chemistry* **2002**, *72*, 1490.

Shibuya, M.; Taniguchi, T.; Takahashi, M.; Ogasawara, K. *Tetrahedron Letters* **2002**, *43*, 4145.

Nesterenko, A. M.; Ponomarenko, M. V.; Lur'e, L. F.; Serguchev, Y. A. *Theoretical and Experimental Chemistry* **2002**, *38*, 156.

Skomorokhov, M. Y.; Klimochkin, Y. N. *Russian Journal of Organic Chemistry* **2001**, *37*, 1188.

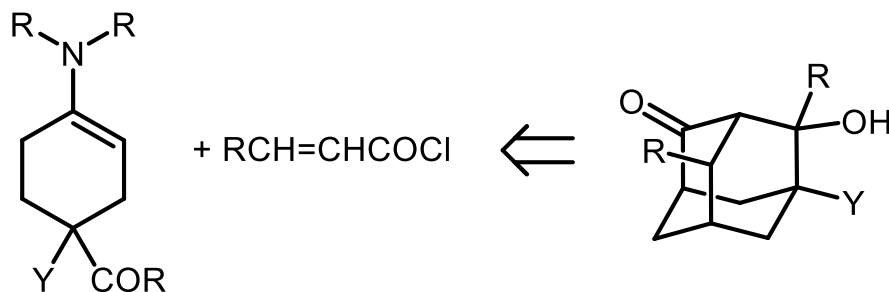
Djaidi, D.; Leung, I. S. H.; Bishop, R.; Craig, D. C.; Scudder, M. L. *Journal of the Chemical Society-Perkin Transactions 1* **2000**, 2037.

Camps, P.; El Achab, R.; Gorbig, D. M.; Morral, J.; Munoz-Torrero, D.; Badia, A.; Banos, J. E.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *Journal of Medicinal Chemistry* **1999**, *42*, 3227.

Denmark, S. E.; Henke, B. R. *Journal of the American Chemical Society* **1989**, *111*, 8032.

Funk, R. L.; Bolton, G. L.; Daggett, J. U.; Hansen, M. M.; Horcher, L. H. M. *Tetrahedron* **1985**, *41*, 3479.

Construction of the adamantane framework from monocyclic compounds



Takagi, R.; Inoue, Y.; Ohkata, K. *Journal of Organic Chemistry* **2008**, *73*, 9320.

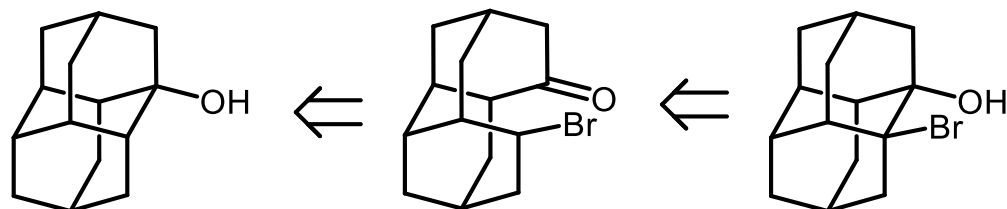
Takagi, R.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Journal of Organic Chemistry* **2005**, *70*, 8587.

Ahmed, M. G.; Ahmed, S. A.; Akhter, K.; Moeiz, S. M. I.; Tsuda, Y.; Kiuchi, F.; Hossain, M. M.; Forsterling, F. H. *Journal of Chemical Research-S* **2005**, 293.

Ahmed, M. G.; Moeiz, S. M. I.; Ahmed, S. A.; Kiuchi, F.; Tsuda, Y.; Sampson, P. *Journal of Chemical Research-S* **1999**, 316.

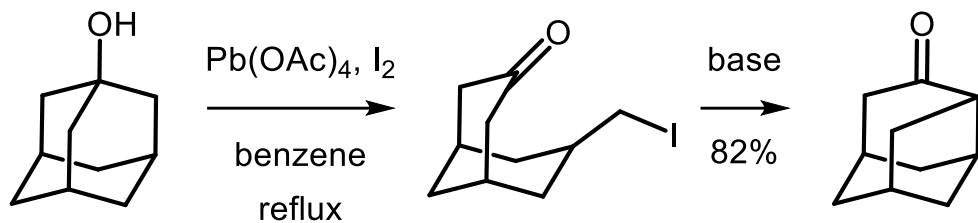
Hickmott, P. W.; Ahmed, M. G.; Ahmed, S. A.; Wood, S.; Kapon, M. *Journal of the Chemical Society-Perkin Transactions 1* **1985**, 2559.

Opening and reconstruction of the diamantane framework

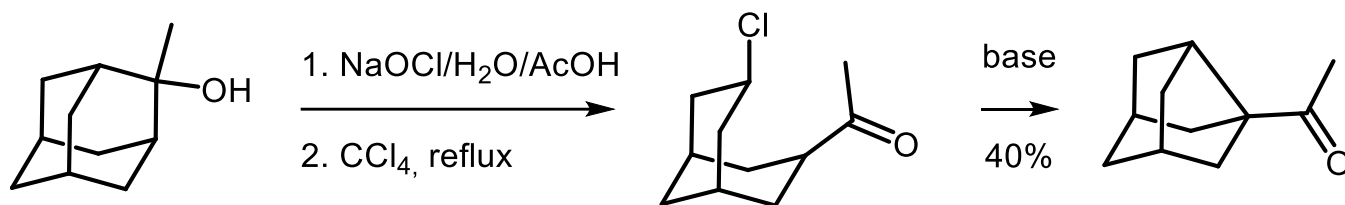


Fokin, A. A.; Pashenko, A. E.; Bakhonsky, V. V.; Zhuk, T. S.; Chernish, L. V.; Gunchenko, P. A.; Kushko, A. O.; Becker, J.; Wende, R. C.; Schreiner, P. R. *Synthesis* **2017**, *49*, 2003.

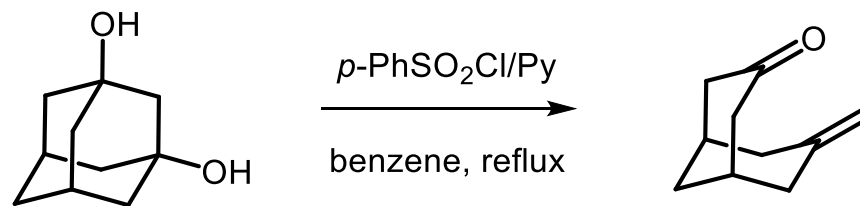
Synthesis of starting materials



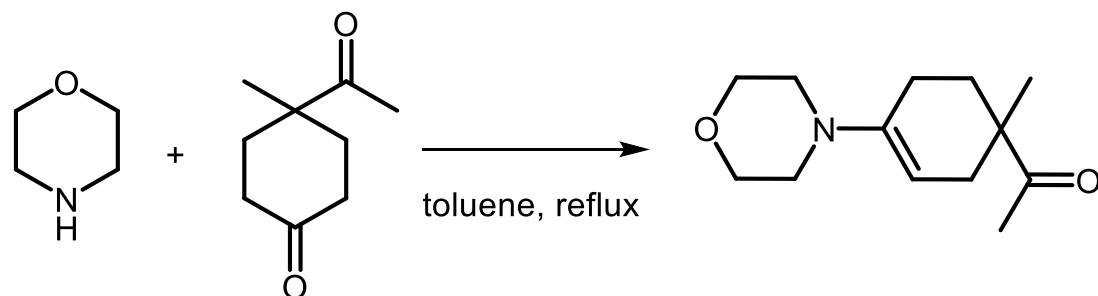
Lenoir, D. *Synthetic communications* **1979**, 9, 103.



Black, R. M.; Gill, G. B. *Chemical communications* **1972**, 972.



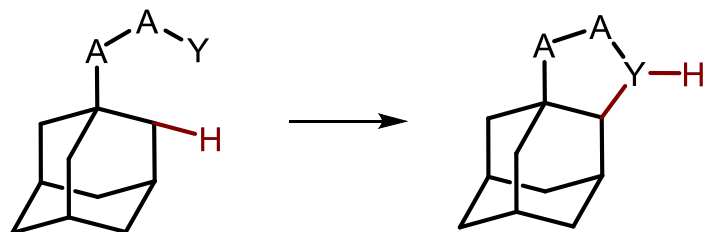
Muraoka, O.; Wang, Y.; Okumura, M.; Nishiura, S.; Tanabea, G.; Momose, T. *Synthetic communications* **1996**, 26, 1555.



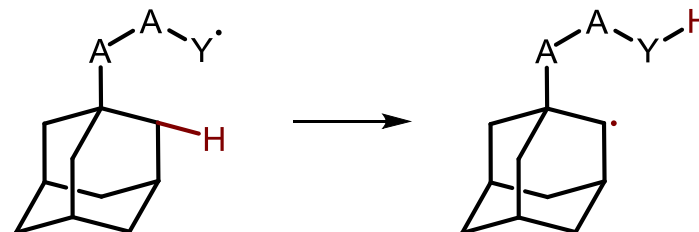
Giasuddin Ahmed, M.; Asghari Ahmed, Syeda; Akhter, Kawsari; Tsuda, Yoshisuke; Mahmum Hossain, M.; Holger Forsterling, F. *Synthetic communications* **2006**, 36, 1273.

Directed C-H functionalization reactions

Insertion reactions



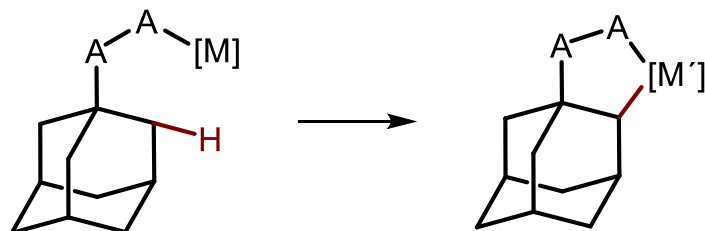
Radical reactions



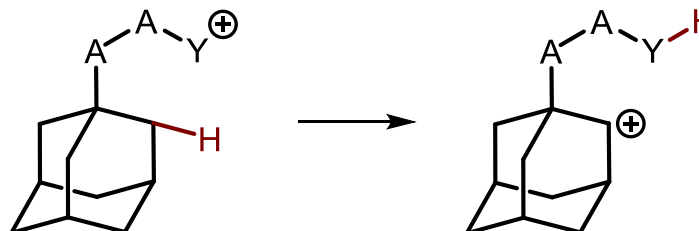
Chu, J. C. K.; Rovis, T. *Angewandte Chemie-International Edition* **2018**, *57*, 62.

Stateman, L. M.; Nakafuku, K. M.; Nagib, D. A. *Synthesis* **2018**, *50*, 1569.

Carbometalations



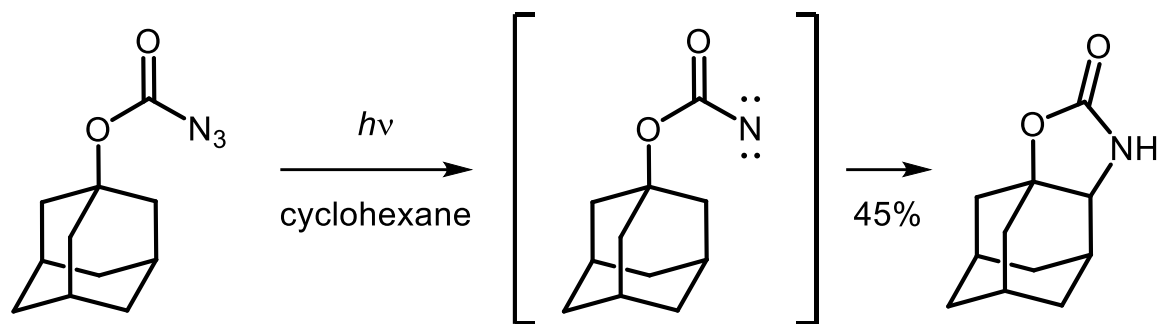
Hydride shift



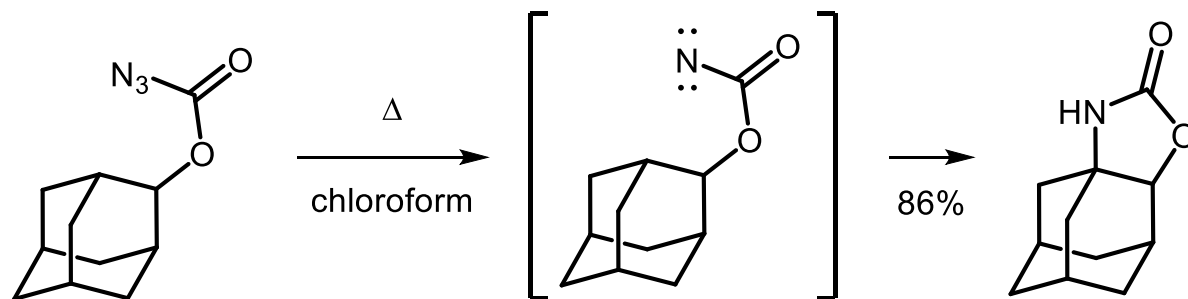
Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chemical Society Reviews* **2016**, *45*, 2900.

Haibach, M. C.; Seidel, D. *Angewandte Chemie-International Edition* **2014**, *53*, 5010.

Insertion reactions



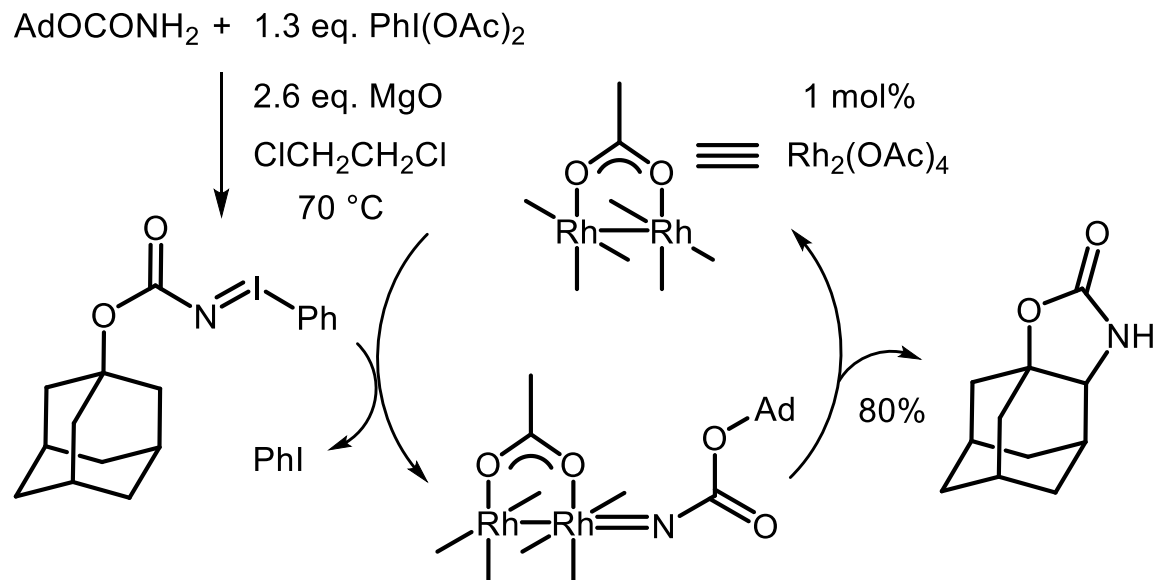
Curran, W. V.; Angier, R. B. *Journal of Organic Chemistry* **1969**, 34, 3668.



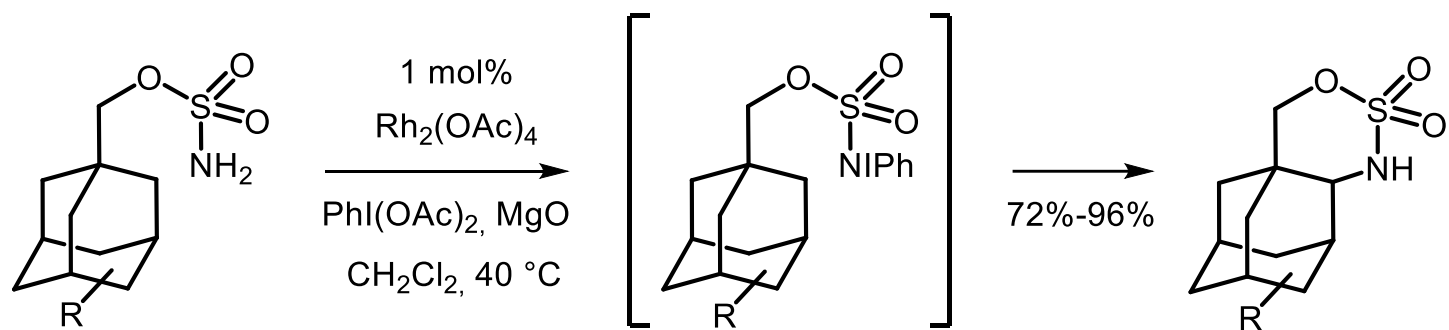
Alewood, P. F.; Benn, M.; Reinfried, R. *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **1974**, 52, 4083.

Insertion reactions

Rohde, J. J.; Pliushchev, M. A.; Sorensen, B. K.; Wodka, D.; Shuai, Q.; Wang, J. H.; Fung, S.; Monzon, K. M.; Chiou, W. J.; Pan, L. P.; Deng, X. Q.; Chovan, L. E.; Ramaiya, A.; Mullally, M.; Henry, R. F.; Stolarik, D. F.; Imade, H. M.; Marsh, K. C.; Beno, W. A.; Fey, T. A.; Droz, B. A.; Brune, M. E.; Camp, H. S.; Sham, H. L.; Frevert, E. U.; Jacobson, P. B.; Link, J. T. *Journal of Medicinal Chemistry* **2007**, *50*, 149.

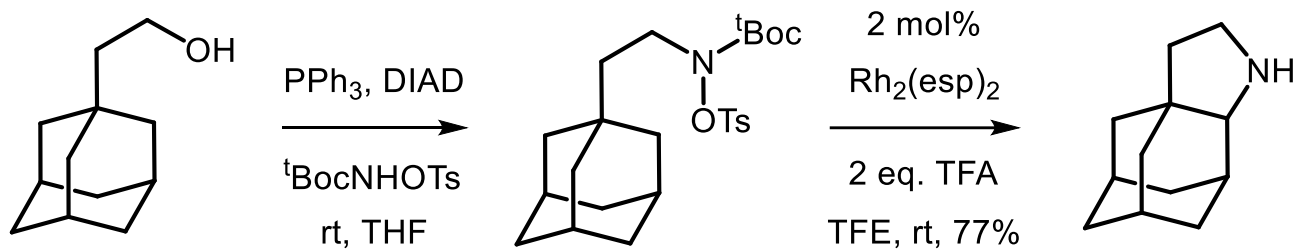


Insertion reactions

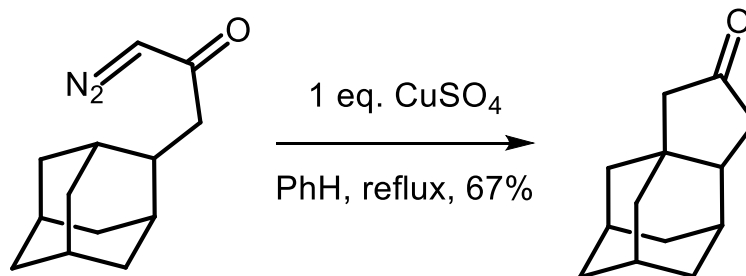


Hrdina, R.; Metz, F. M.; Larrosa, M.; Berndt, J. P.; Zhygado, Y. Y.; Becker, S.; Becker, J. *European Journal of Organic Chemistry* **2015**, 6231.

Insertion reactions

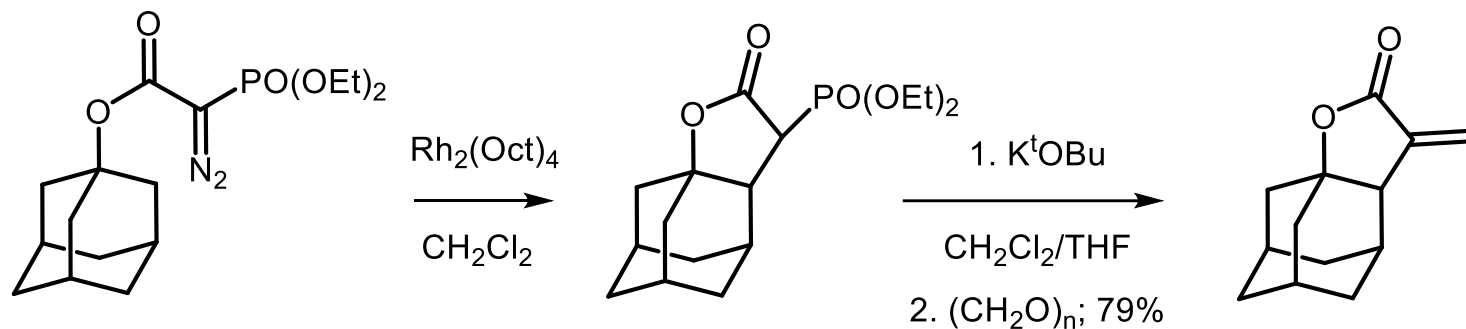


Munnuri, S.; Adebessin, A. M.; Paudyal, M. P.; Yousufuddin, M.; Dalipe, A.; Falck, J. R. *Journal of the American Chemical Society* **2017**, *139*, 18288.

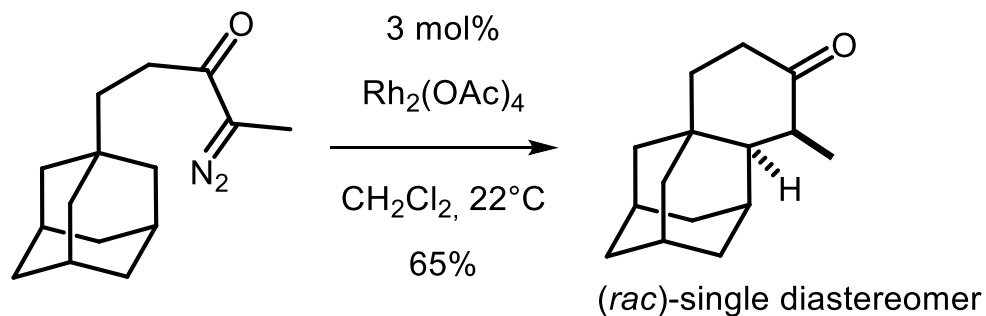


Osawa, E.; Tahara, Y.; Togashi, A.; Iizuka, T.; Tanaka, N.; Kan, T.; Farcasiu, D.; Kent, G. J.; Engler, E. M.; Schleyer, P. v. R. *Journal of Organic Chemistry* **1982**, *47*, 1923.

Insertion reactions

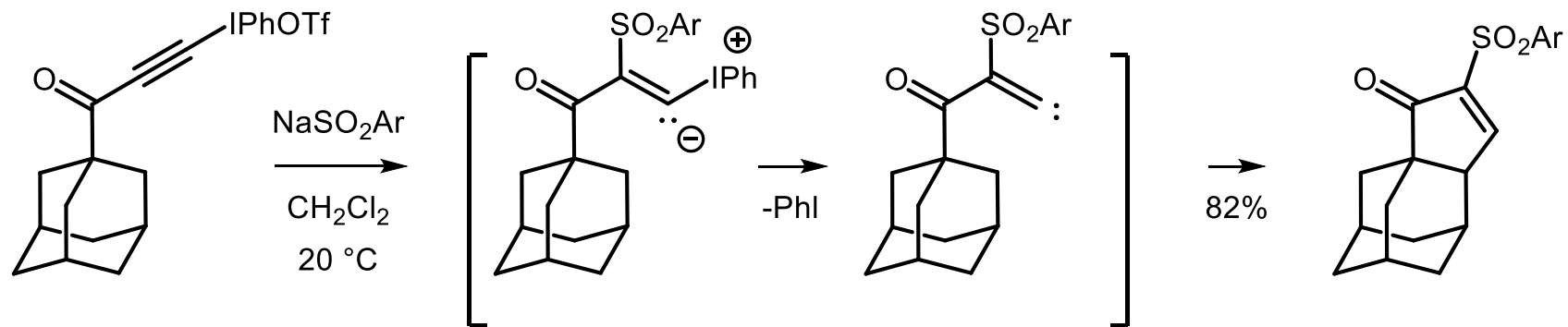


Lloyd, M. G.; D'Acunto, M.; Taylor, R. J. K.; Unsworth, W. P. *Tetrahedron* **2015**, *71*, 7107.

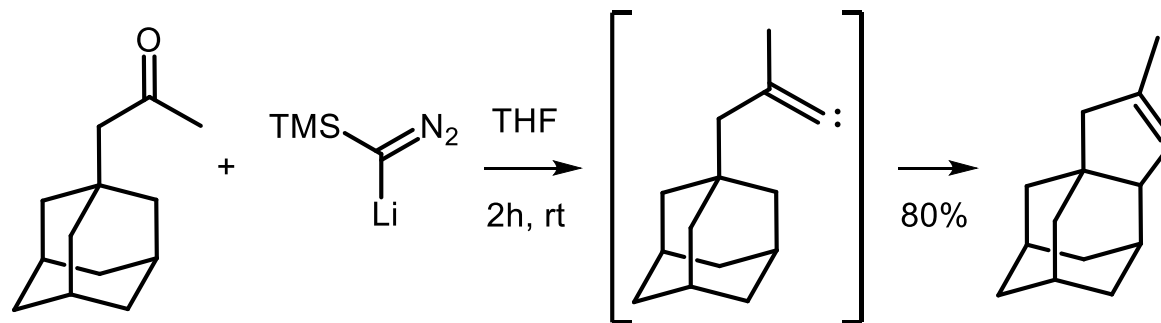


Nicolaou, K. C.; Stepan, A. F.; Lister, T.; Li, A.; Montero, A.; Tria, G. S.; Turner, C. I.; Tang, Y. F.; Wang, J. H.; Denton, R. M.; Edmonds, D. J. *Journal of the American Chemical Society* **2008**, *130*, 13110.

Insertion reactions

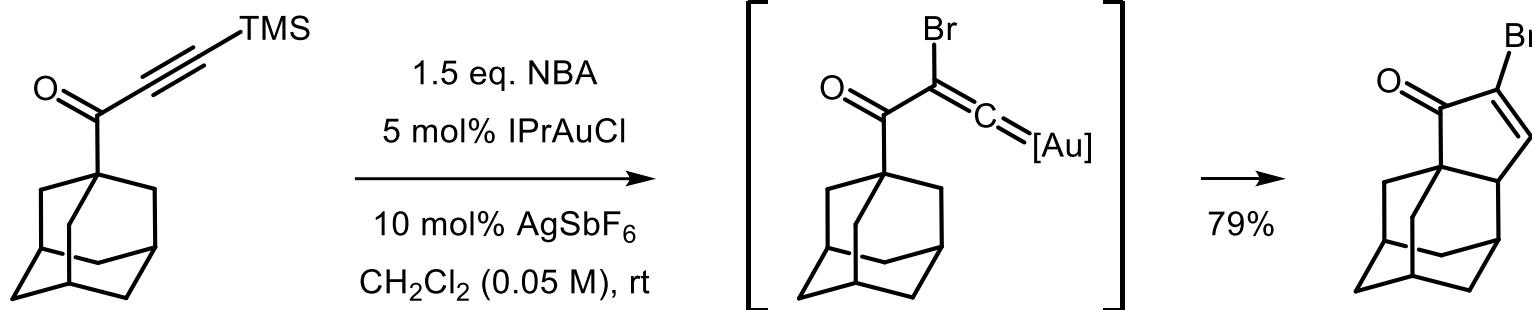


Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *Journal of the American Chemical Society* **1994**, 116, 93.



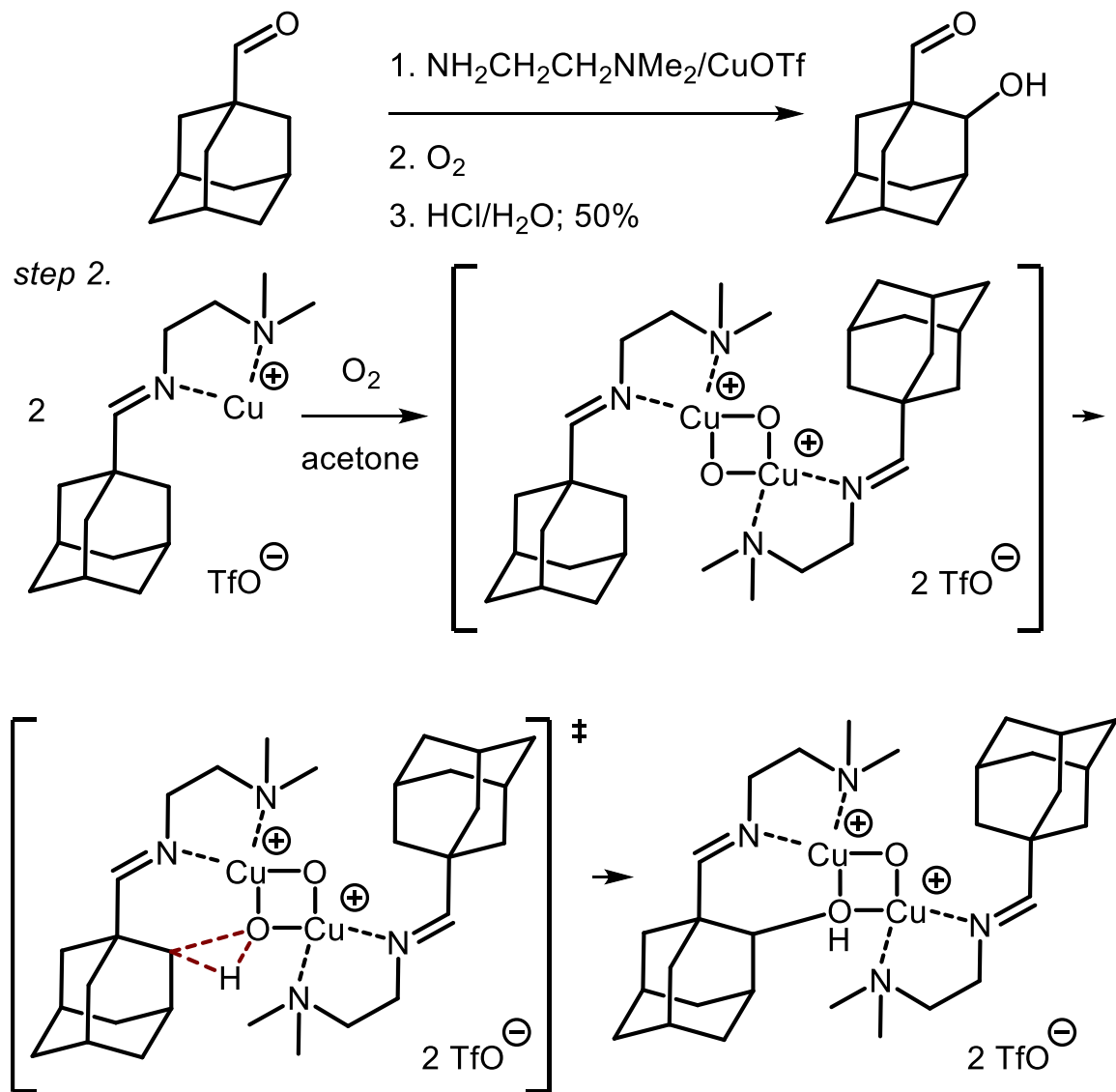
Zheng, J. C.; Yun, S. Y.; Sun, C. R.; Lee, N. K.; Lee, D. *Journal of Organic Chemistry* **2011**, 76, 1086.

Insertion reactions

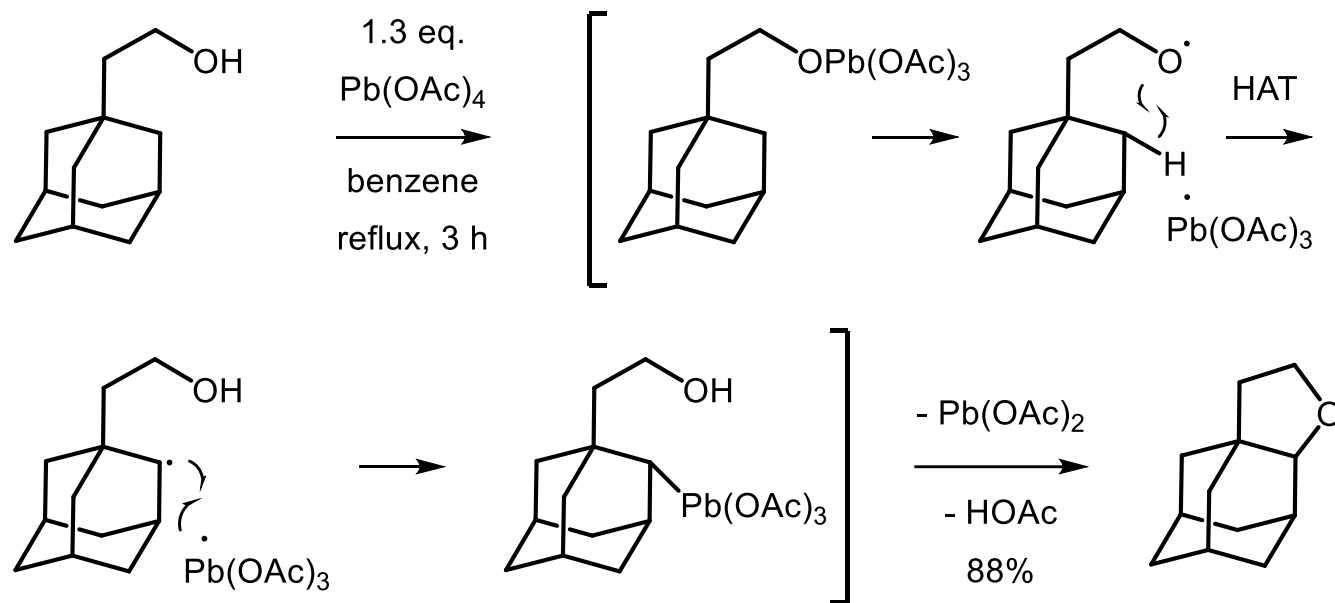


Wang, Y. L.; Zarca, M.; Gong, L. Z.; Zhang, L. M. *Journal of the American Chemical Society* **2016**, *138*, 7516.

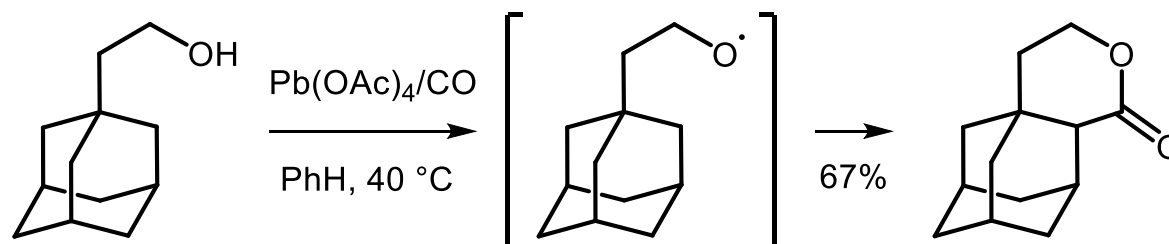
Insertion reactions



Hydrogen radical abstraction reactions

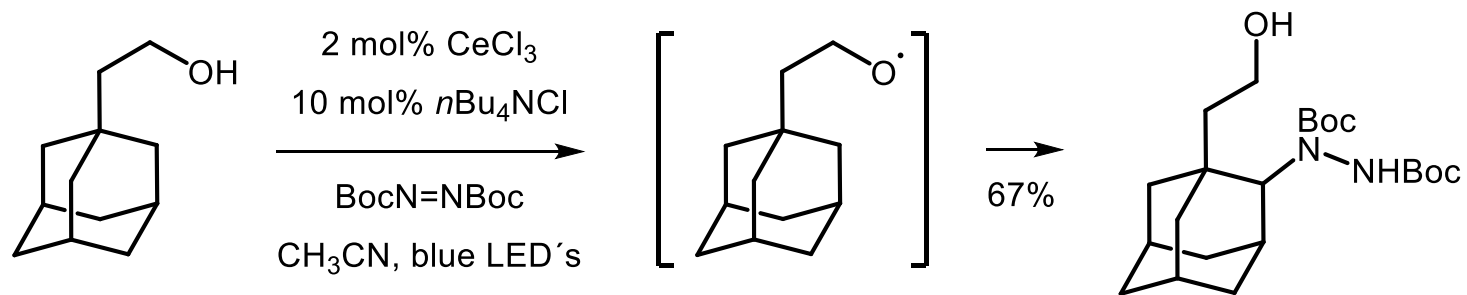


Lunn, W. H. W.; Podmore, W. D.; Szinai, S. S. *Journal of the Chemical Society C-Organic* **1968**, 1657.

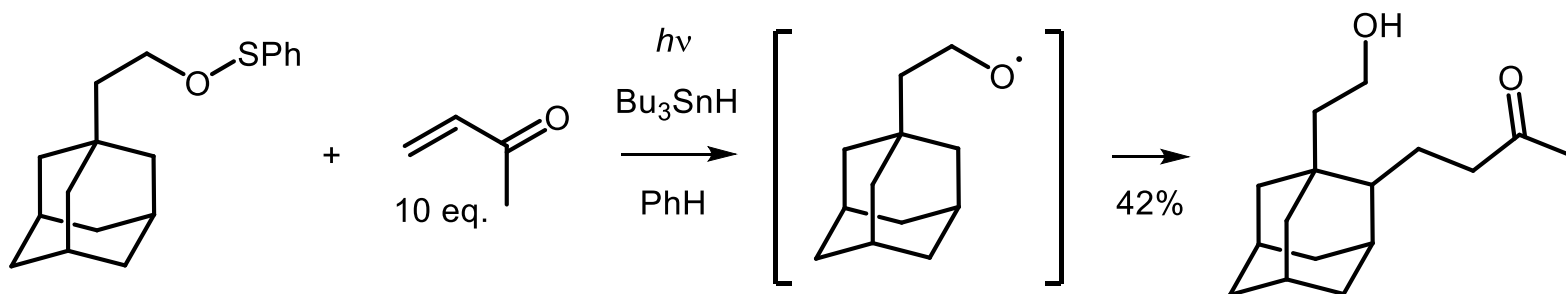


Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Journal of the American Chemical Society* **1998**, 120, 8692.

Hydrogen radical abstraction reactions

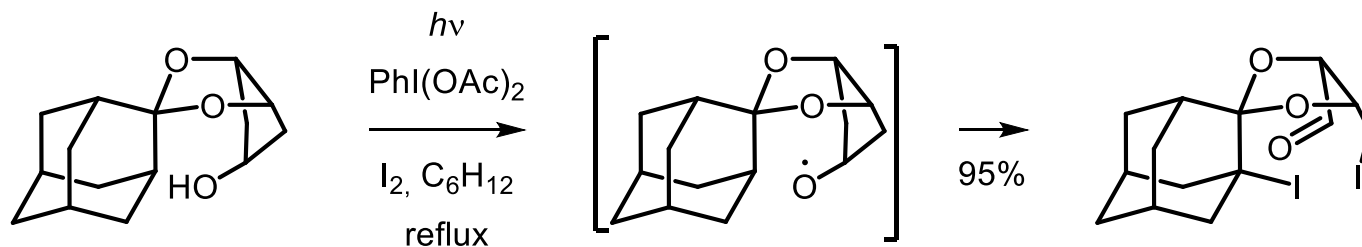


Hu, A. H.; Guo, J. J.; Pan, H.; Tang, H. M.; Gao, Z. B.; Zuo, Z. W. *Journal of the American Chemical Society* **2018**, *140*, 1612.

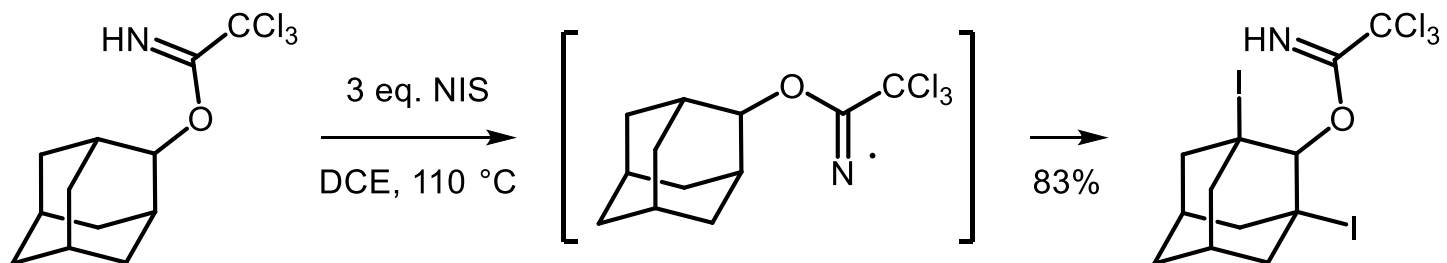


Petrovic, G.; Cekovic, Z. *Organic Letters* **2000**, *2*, 3769.

Hydrogen radical abstraction reactions

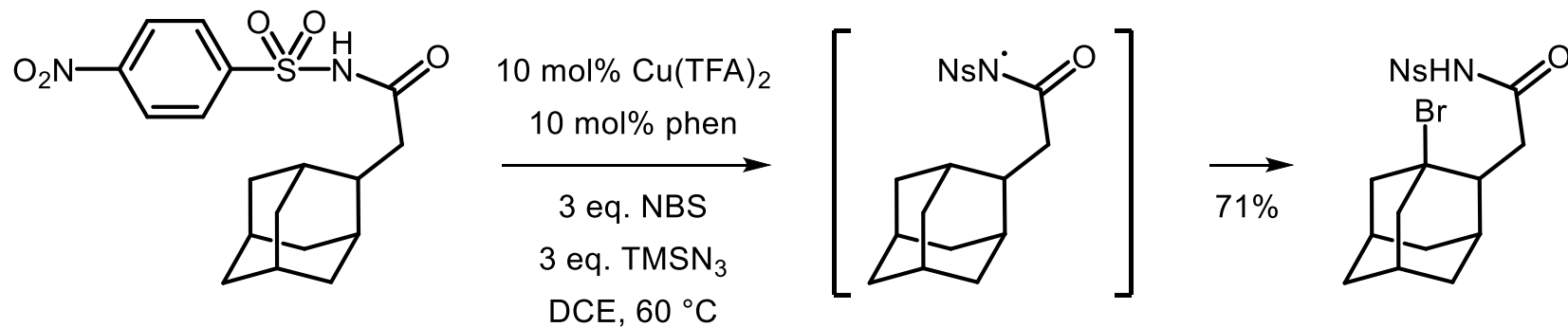


Spitz, U. P.; Eaton, P. E. *Angewandte Chemie-International Edition in English* **1994**, 33, 2220.

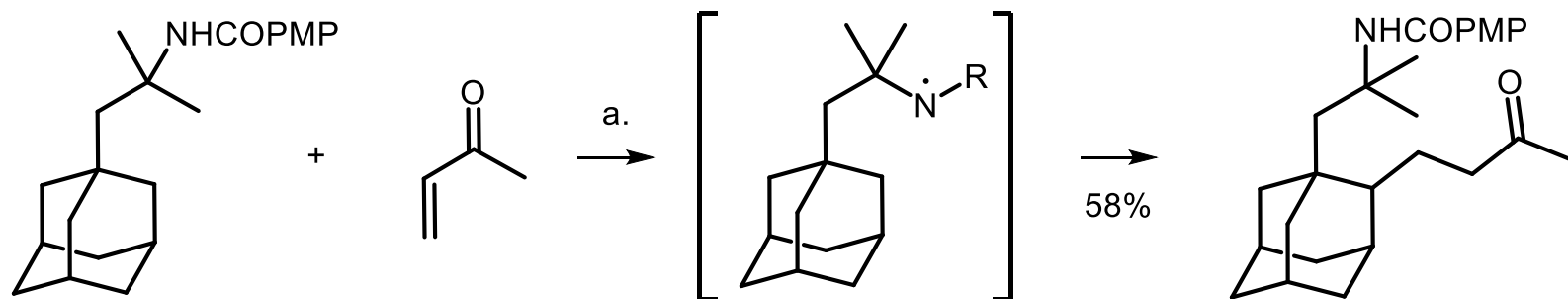


Mou, X. Q.; Chen, X. Y.; Chen, G.; He, G. *Chemical Communications* **2018**, 54, 515.

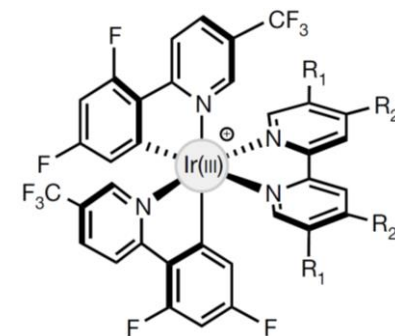
Hydrogen radical abstraction reactions



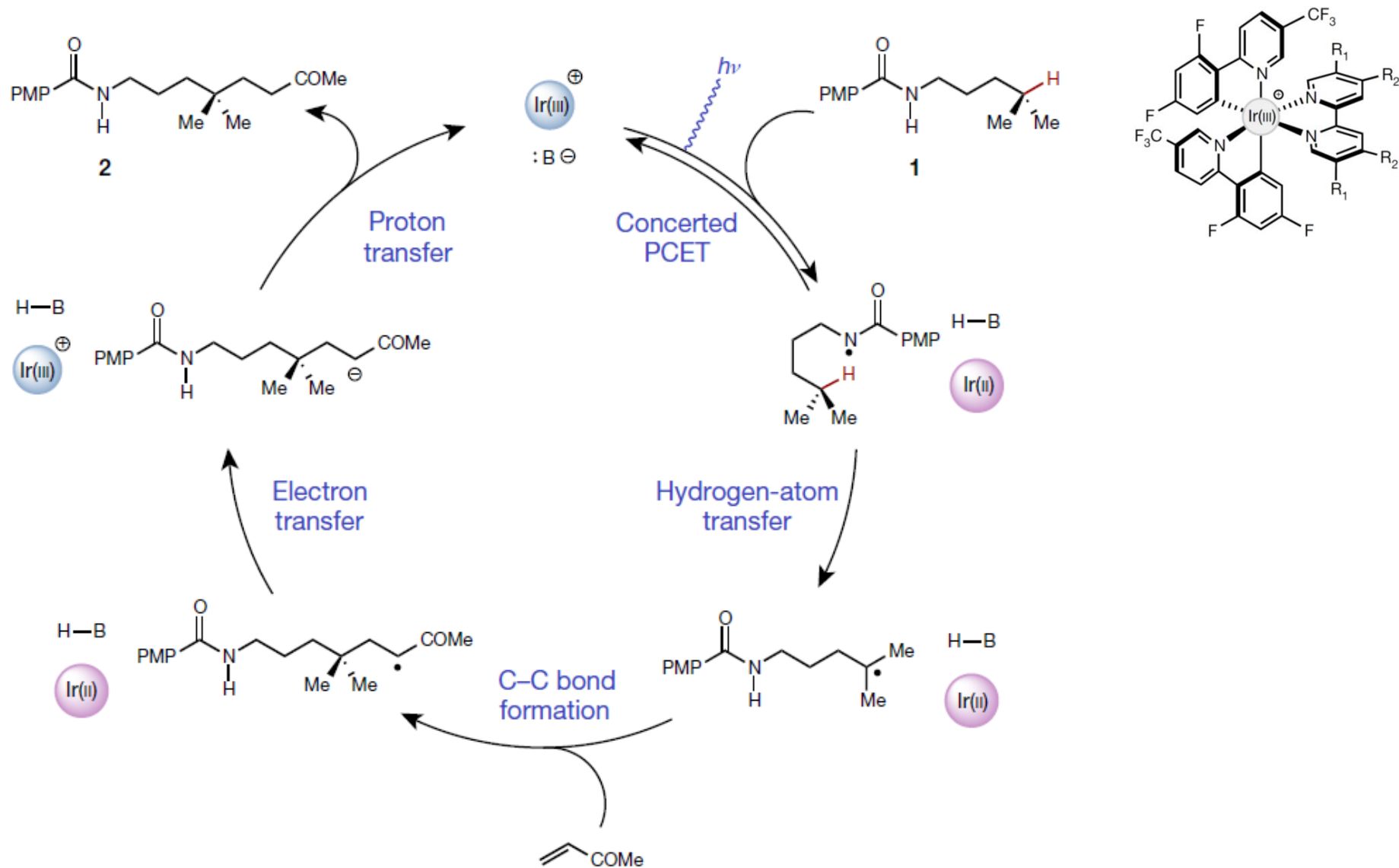
Liu, T.; Myers, M. C.; Yu, J. Q. *Angewandte Chemie-International Edition* **2017**, 56, 306.



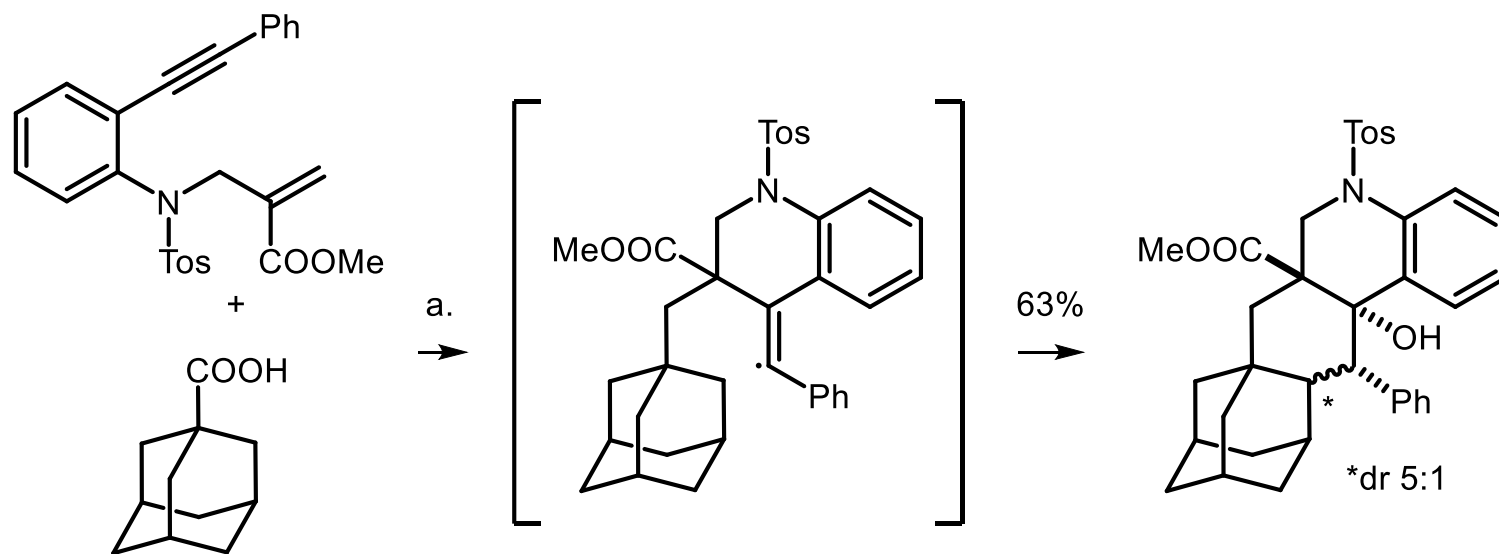
a) 2 mol% [Ir(dF(CF₃)ppy)₂(5,5'-d(CF₃)bpy)] PF₆,
5 mol% NBu₄OPO(OBu)₂, 0.2M PhCF₃, blue LEDs, rt
R=NHCOPMP=NHCO(*p*-OMe-Ph)



Hydrogen radical abstraction reactions



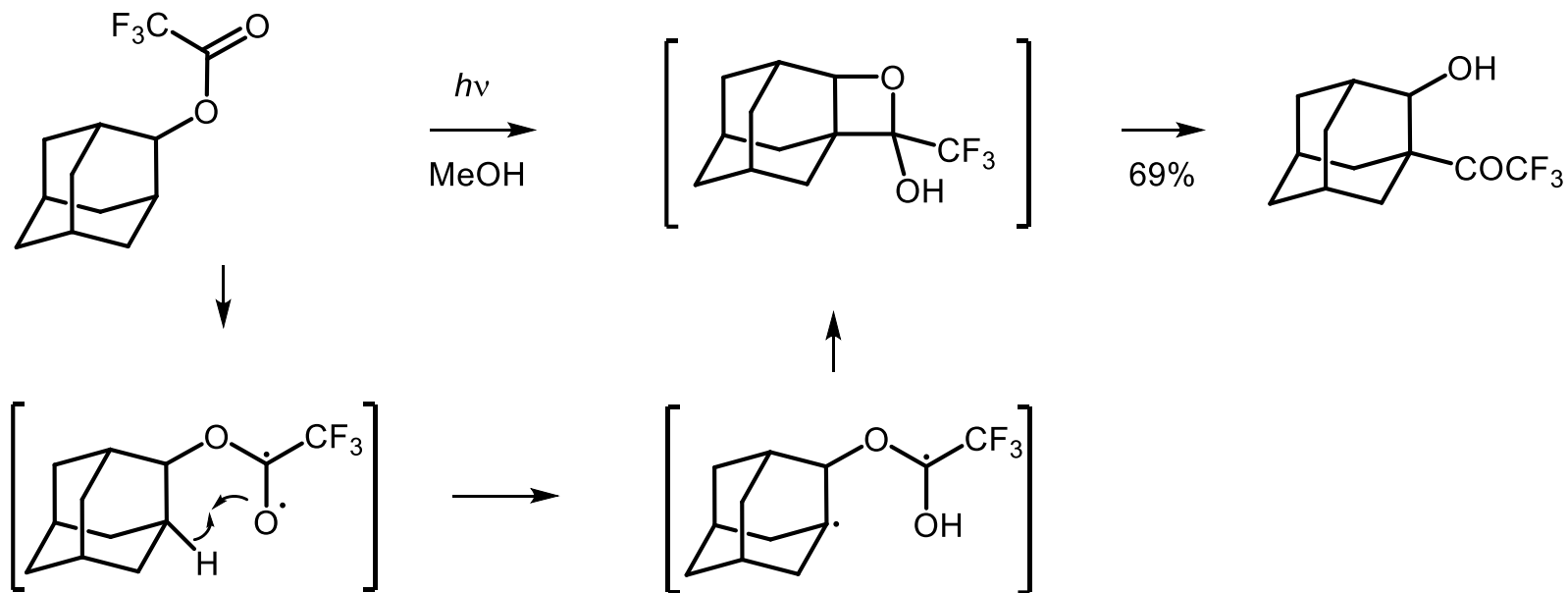
Hydrogen radical abstraction reactions



a) 20 mol% $\text{Ag}(\text{NO}_3)$, 1.5 eq. $\text{K}_2\text{S}_2\text{O}_8$, $\text{MeCN}/\text{H}_2\text{O}$ 2:1;

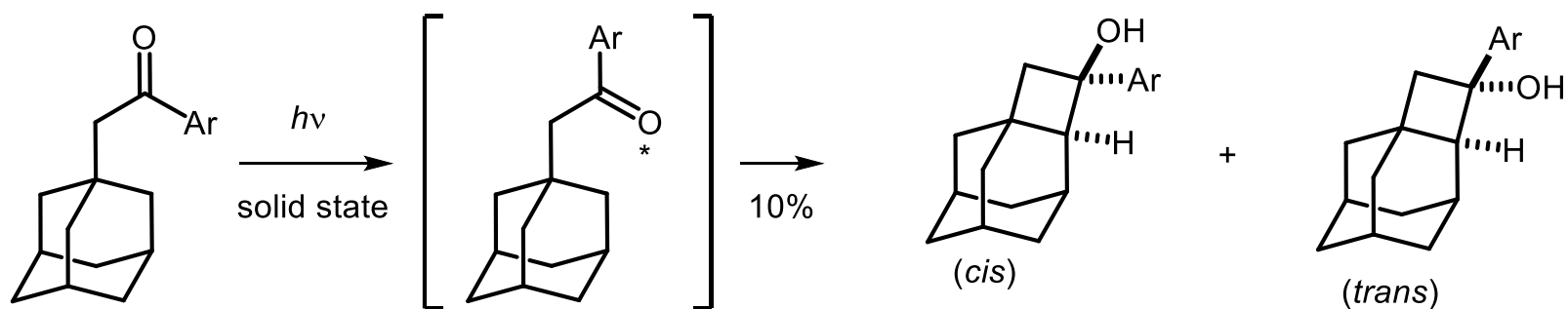
Lv, L. Y.; Li, Z. P. *Journal of Organic Chemistry* **2017**, *82*, 2689.

Hydrogen radical abstraction reactions



Marron, N. A.; Gano, J. E. *Synthetic Communications* **1977**, *7*, 515.

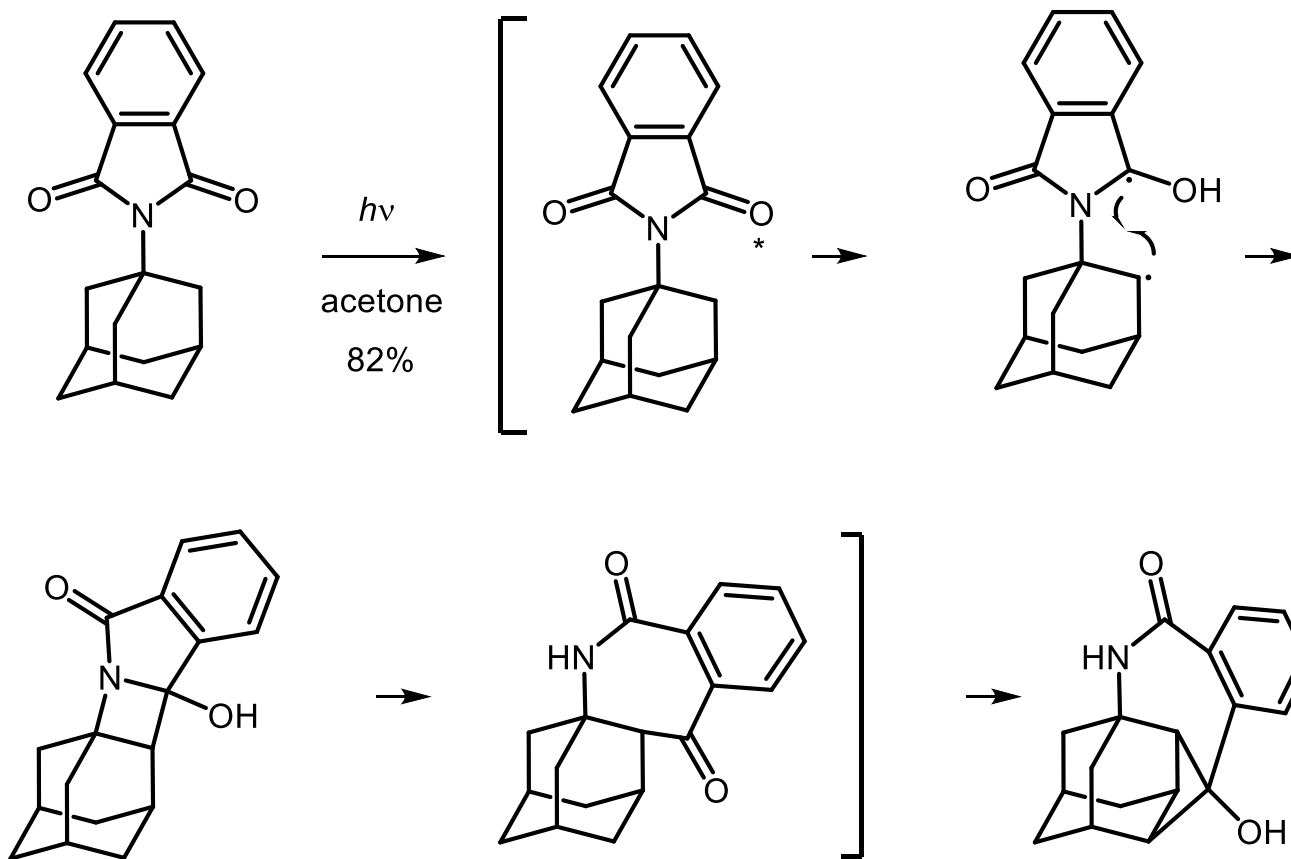
Hydrogen radical abstraction reactions



needles: cis/trans 26:74
plates: cis/trans 0:100

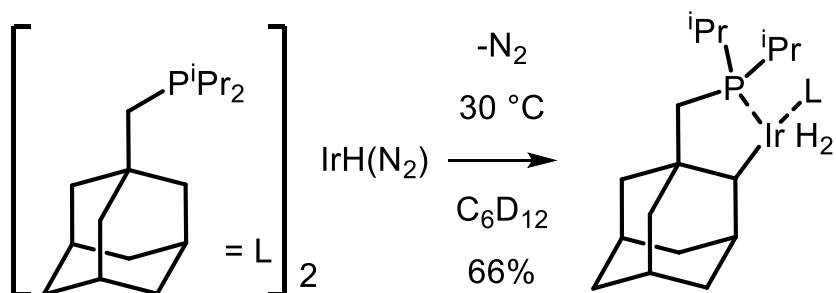
Evans, S.; Omkaram, N.; Scheffer, J. R.; Trotter, J. *Tetrahedron Letters* **1985**, 26, 5903.

Hydrogen radical abstraction reactions

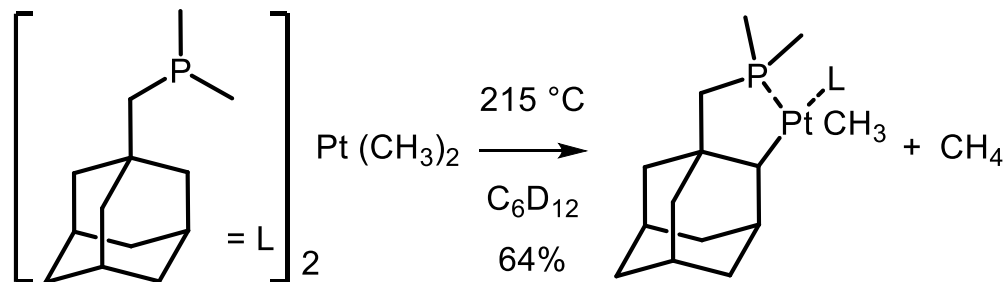


Basaric, N.; Horvat, M.; Mlinaric-Majerski, K.; Zimmermann, E.; Neudorfl, J.; Griesbeck, A. G. *Organic Letters* **2008**, *10*, 3965.

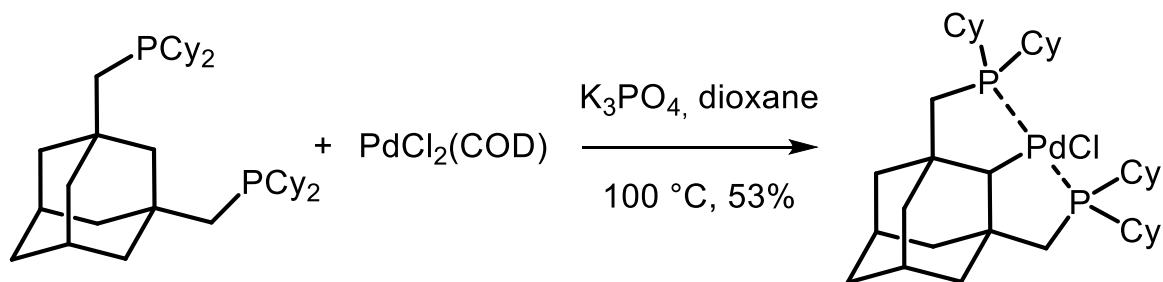
Carbometalations



Millard, M. D.; Moore, C. E.; Rheingold, A. L.; Figueroa, J. S. *Journal of the American Chemical Society* **2010**, *132*, 8921.

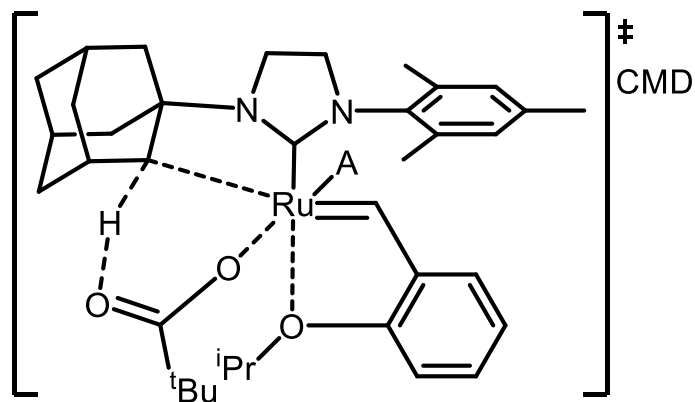
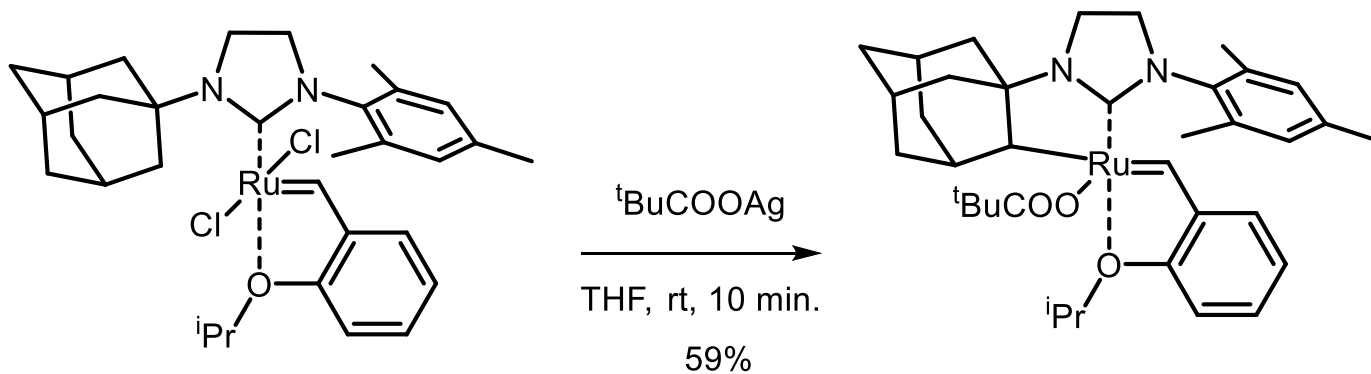


Hackett, M.; Whitesides, G. M. *Organometallics* **1987**, *6*, 403.



Gerber, R.; Blacque, O.; Frech, C. M. *Chem.Cat.Chem.* **2009**, *1*, 393.

Carbometalations

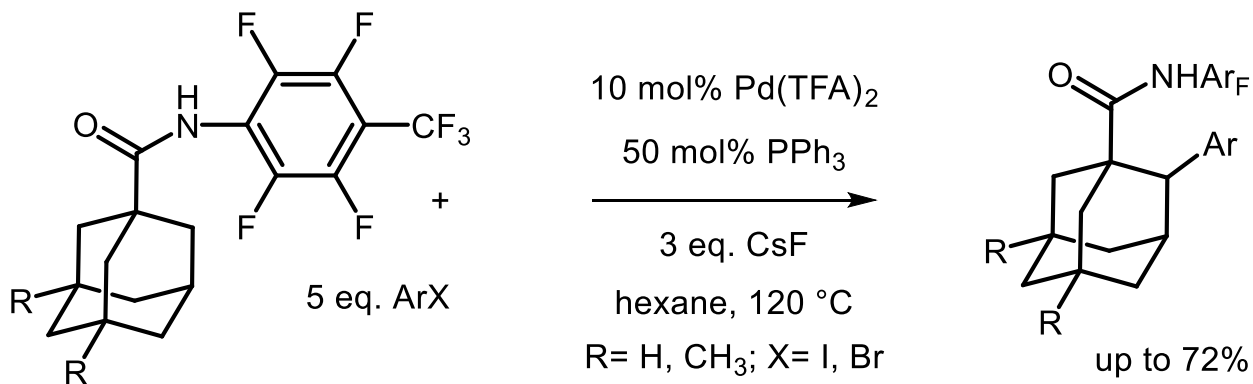


Cannon, J. S.; Zou, L. F.; Liu, P.; Lan, Y.; O'Leary, D. J.; Houk, K. N.; Grubbs, R. H. *Journal of the American Chemical Society* **2014**, *136*, 6733.

Carbometalations in catalysis

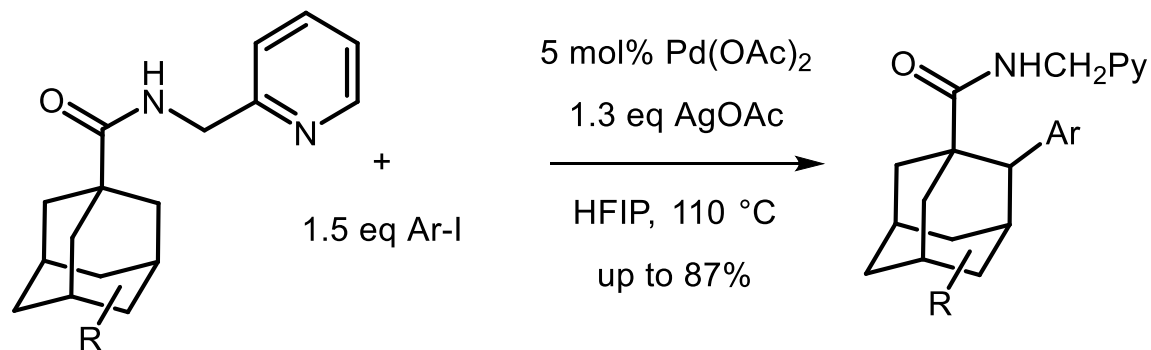


Pan, J. L.; Li, Q. Z.; Zhang, T. Y.; Hou, S. H.; Kang, J. C.; Zhang, S. Y. *Chemical Communications* **2016**, 52, 13151.

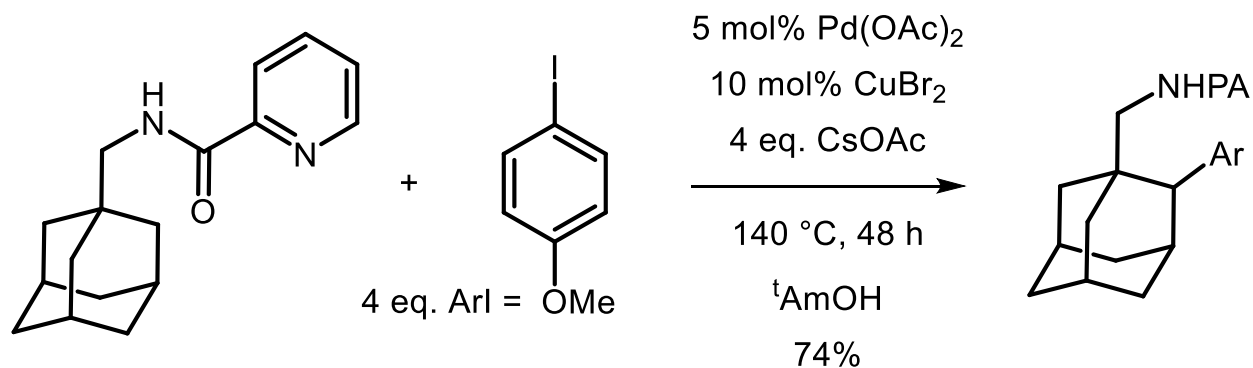


Lao, Y. X.; Wu, J. Q.; Chen, Y. Y.; Zhang, S. S.; Li, Q. J.; Wang, H. G. *Organic Chemistry Frontiers* **2015**, 2, 1374.

Carbometalations in catalysis

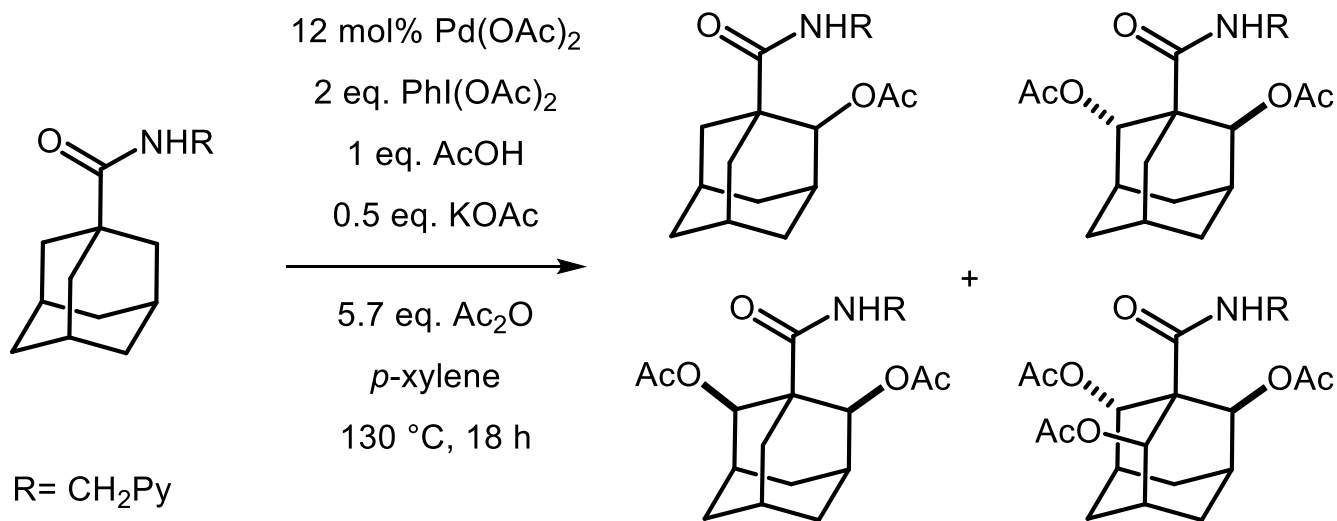


Larrosa, M.; Heiles, S.; Becker, J.; Spengler, B.; Hrdina, R. *Advanced Synthesis & Catalysis* **2016**, 358, 2163.



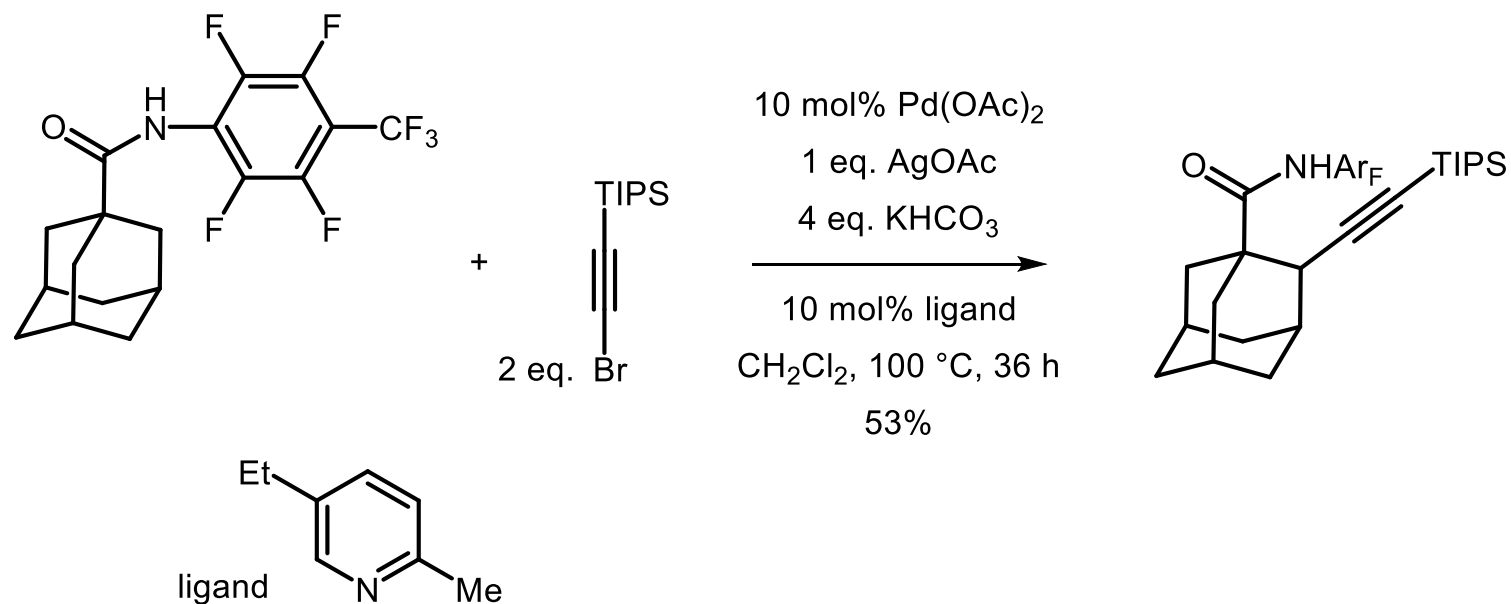
Coomber, C. E.; Benhamou, L.; Bucar, D. K.; Smith, P. D.; Porter, M. J.; Sheppard, T. D. *Journal of Organic Chemistry* **2018**, 83, 2495-2503

Carbometalations in catalysis



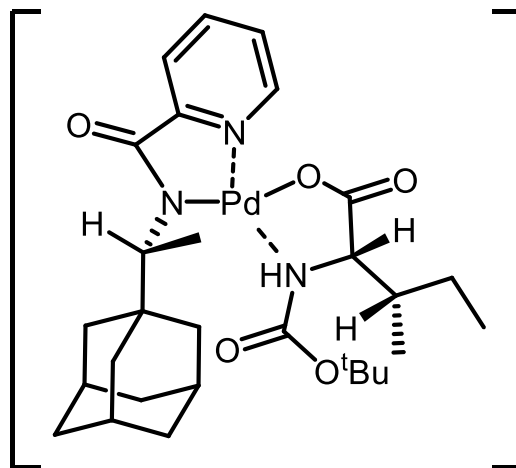
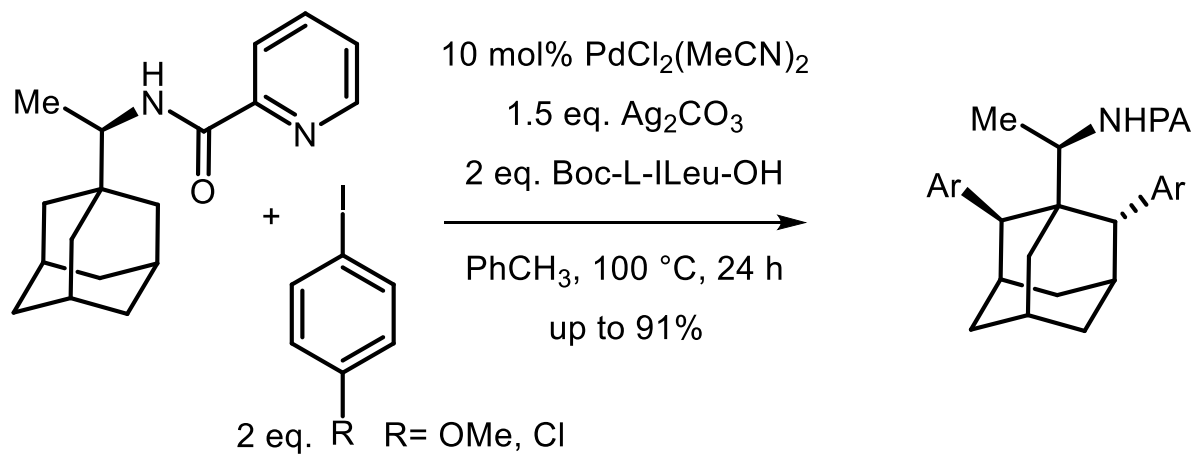
Larrosa, M.; Zonker, B.; Volkmann, J.; Wech, F.; Logemann, C.; Hausmann, H.; Hrdina, R. *Chemistry-a European Journal* **2018**, *24*, 6269.

Carbometalations in catalysis



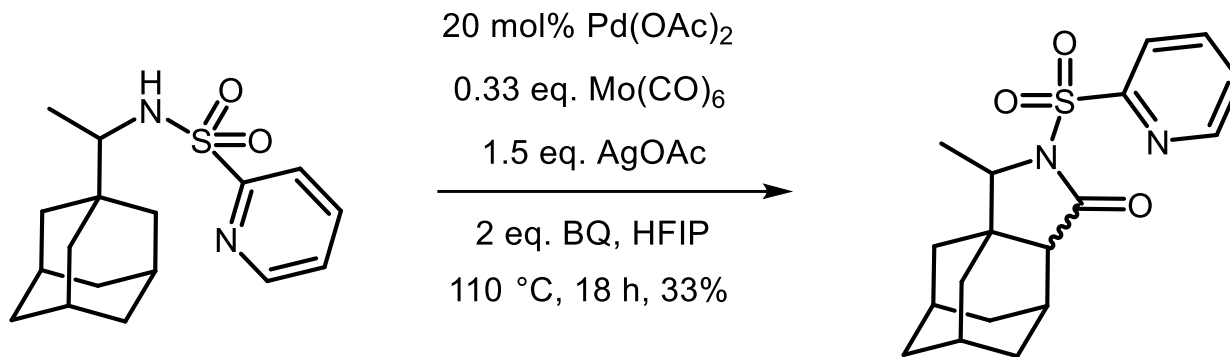
Fu, H. Y.; Shen, P. X.; He, J.; Zhang, F. L.; Li, S. H.; Wang, P.; Liu, T.; Yu, J. Q. *Angewandte Chemie-International Edition* **2017**, *56*, 1873.

Carbometalations in catalysis

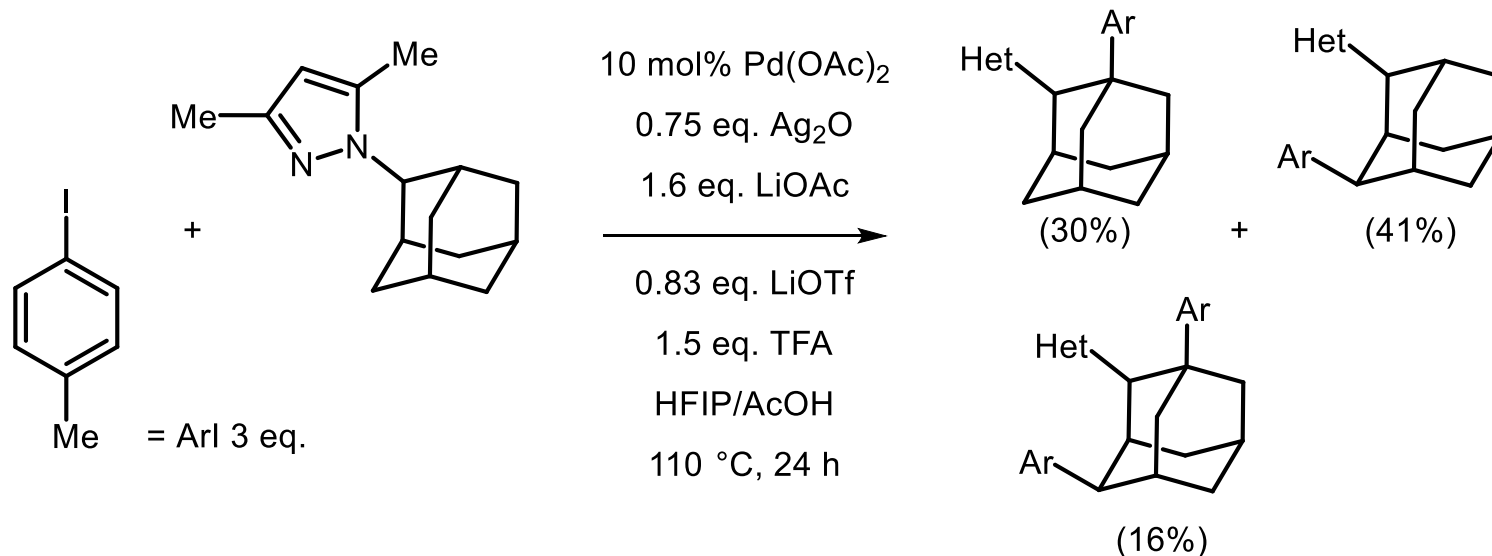


Fan, Z. L.; Shu, S. Q.; Ni, J. B.; Yao, Q. Z.; Zhang, A. *ACS Catalysis* **2016**, *6*, 769.

Carbometalations in catalysis

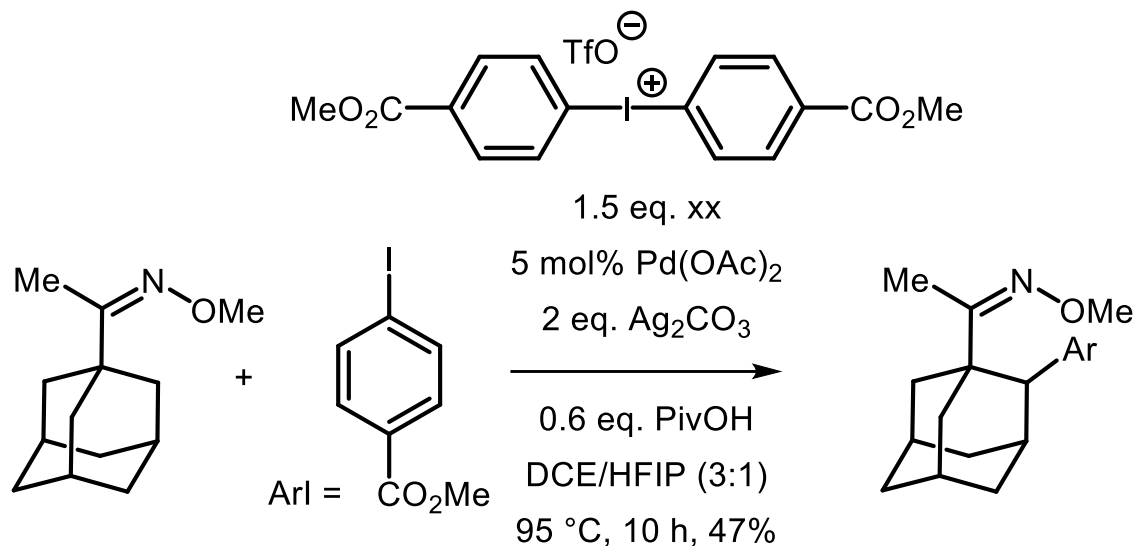


Hernando, E.; Villalva, J.; Martinez, A. M.; Alonso, I.; Rodriguez, N.; Arrayas, R. G.; Carretero, J. C. *ACS Catalysis* **2016**, *6*, 6868.

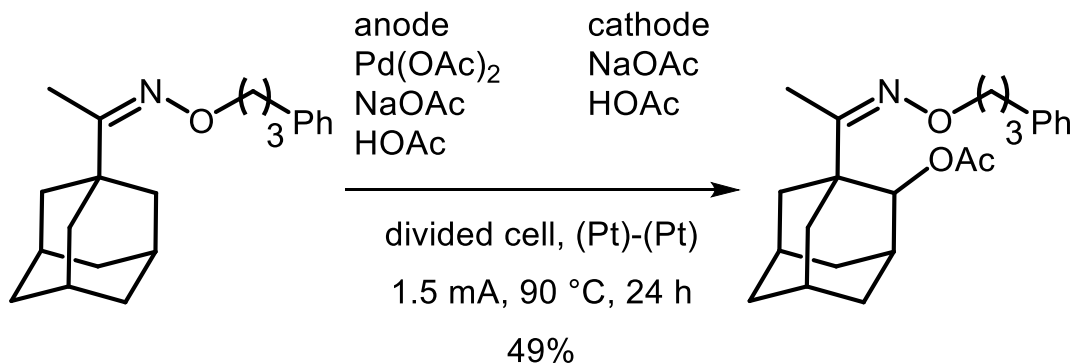


Gulia, N.; Daugulis, O. *Angewandte Chemie-International Edition* **2017**, *56*, 3630.

Carbometalations in catalysis

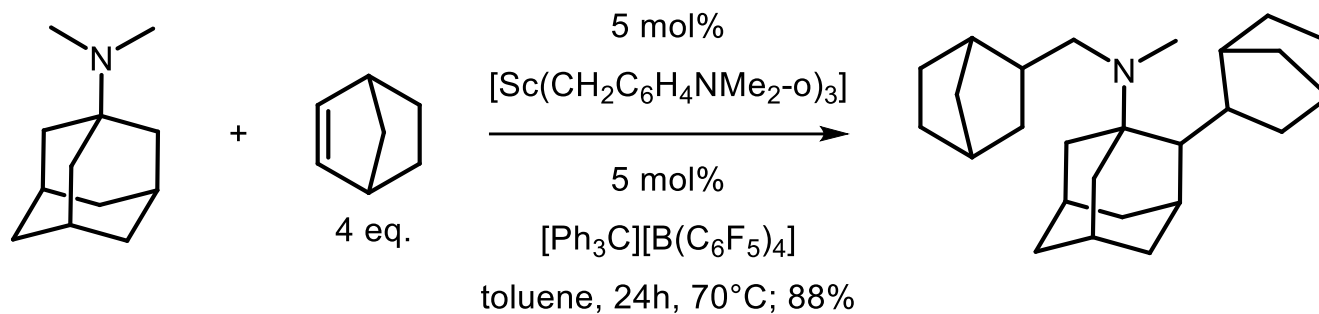


Peng, J.; Chen, C.; Xi, C. J. *Chemical Science* **2016**, 7, 1383.

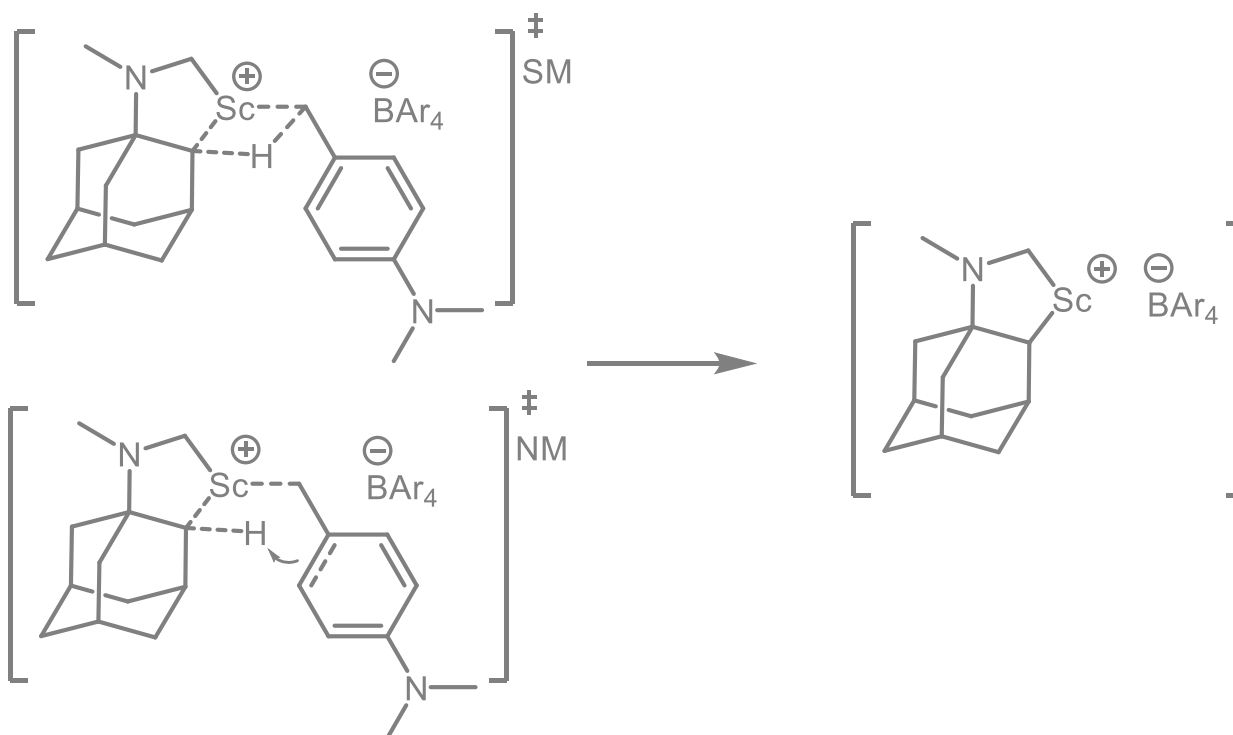


Yang, Q. L.; Li, Y. Q.; Ma, C.; Fang, P.; Zhang, X. J.; Mei, T. S. *Journal of the American Chemical Society* **2017**, 139, 3293.

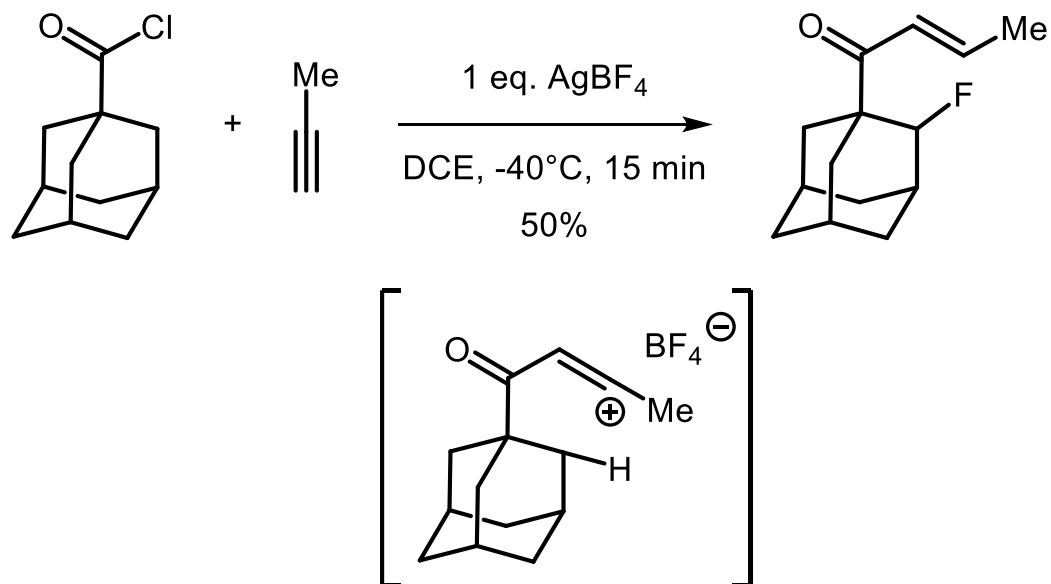
Carbometalations in catalysis



Nako, A. E.; Oyamada, J.; Nishiura, M.; Hou, Z. M. *Chemical Science* **2016**, 7, 6429.

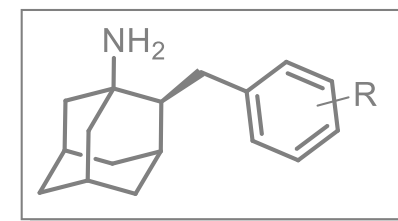
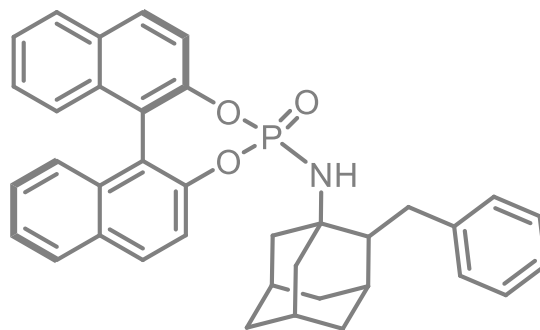
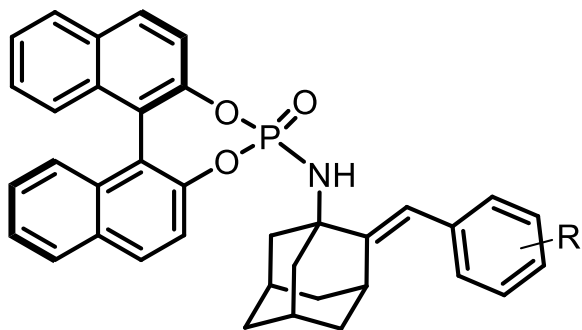
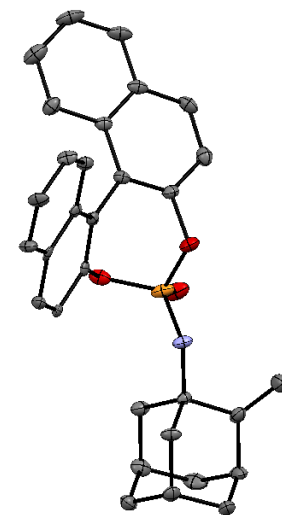
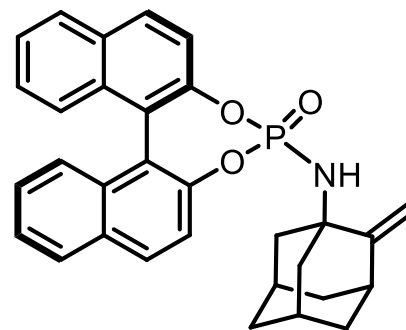
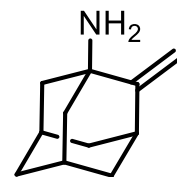
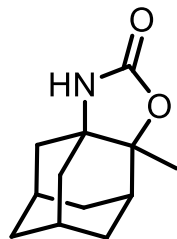
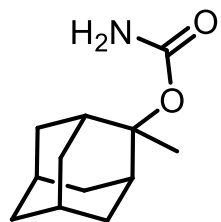
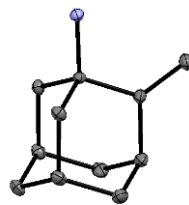
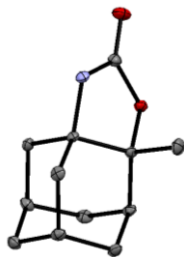
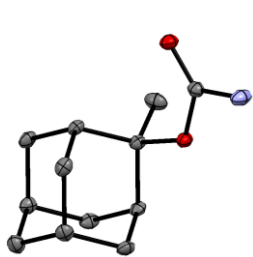


Hydride shift

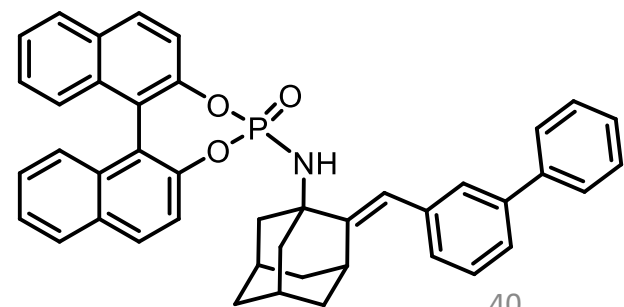
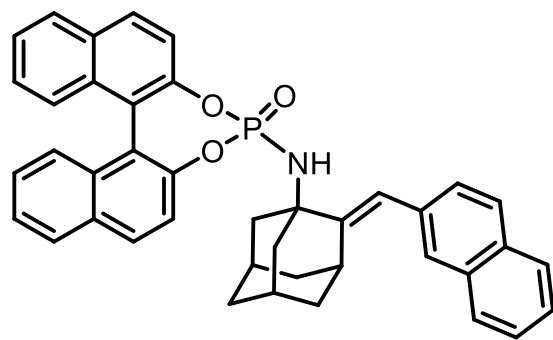
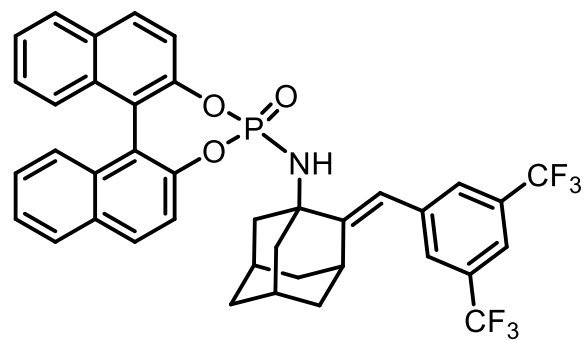
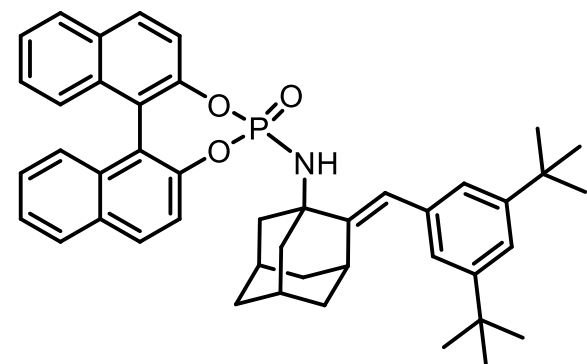
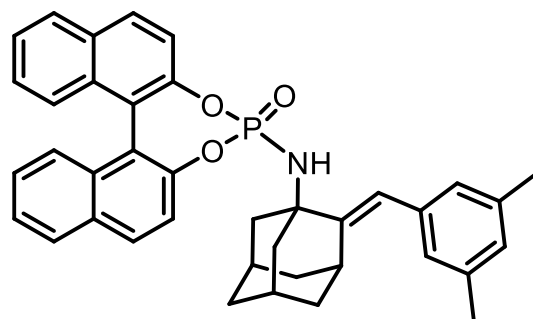
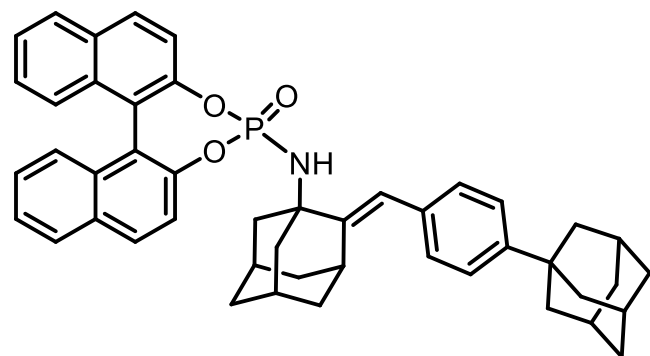
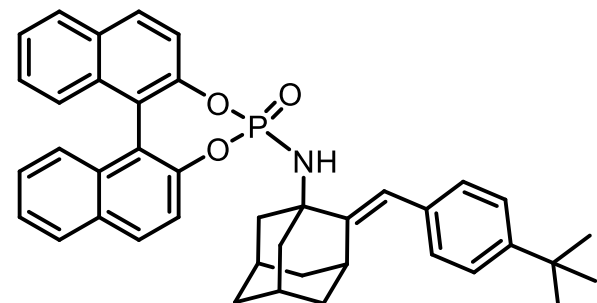
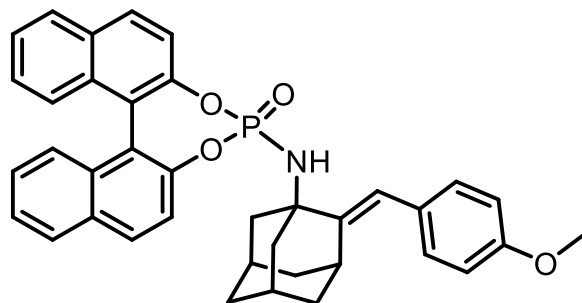
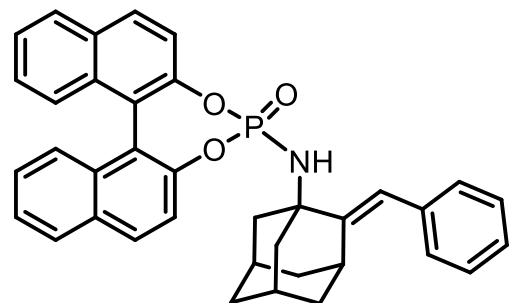


Kanishchev, M. I.; Smit, V. A.; Shchegolev, A. A.; Rodionov, A. P.; Caple, R. *Bulletin of the Academy of Sciences of the USSR Division of Chemical Science* **1979**, 28 (4), 778-784.

Almost there



State of the art



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