Published in final edited form as:

Angew Chem Int Ed Engl. 2012 August 20; 51(34): 8602–8606. doi:10.1002/anie.201203521.

An Expeditious Route to Eight-Membered Heterocycles By Nickel-Catalyzed Cycloaddition: Low Temperature C(sp²)-C(sp³) Bond Cleavage**

Puneet Kumar, Kainan Zhang, and Janis Louie*

Department of Chemistry, University of Utah, 315 South, 1400 East, Salt Lake City, Utah 84112-0850

Keywords

C-C activation; cycloaddition; nickel; catalyst; diynes; azetidinones; azocines

At the onset of 21st century, chemists have witnessed an immense growth in the field of C-H activation, which offers an elegant solution to a cleaner construction of a C-C bond by minimizing waste.^[1] Alternatively, C-C bond activation provides another possible solution to the aforementioned problem. Although significant progress has been made in the area of C-H activation, C-C bond activation is still relatively dormant.^[2] The reason can be attributed to the highly inert nature of C-C sigma bond in addition to a poor interaction of the orbitals of C-C sigma bond and transition metals.^[2a]

A significant amount of literature has been reported on utilizing the inherent strain of cyclopropanes (strain energy = 27.6 kcal/mol) by transition-metal catalysts.^[3] In comparison to this, cyclobutanes (strain energy = 26.4 kcal/mol) remained largely unexplored until the remarkable finding by Murakami and co-workers.^[4] Since then appreciable efforts have been made in harnessing the latent potential of cyclobutanones by various transition-metal catalysts.^[5] Most of these studies revolve around developing methods to access carbocycles that are otherwise difficult to synthesize.

(1)

Our group has been active in developing new nickel-catalyzed cycloaddition reactions. Recently, we and others independently discovered a Ni/PPh₃ catalyzed method for coupling azetidinones and alkynes to afford 3-piperidones, which involves cleavage of the C-C bond

The NIH and the NSF are acknowledged for financial support. We thank Dr. J. Muller and Dr. A. Aarif of the University of Utah for providing HRMS and single crystal X-ray crystallographic data, respectively. We also thank Mr. Ashish Thakur for the preparation of diynes **1g, **1h**, and partial synthesis of **1m**.

*louie@chem.utah.edu, Homepage : <http://www.chem.utah.edu/faculty/louie/index.html>.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

between the carbonyl and a methylene of the azetidinone.^[6] We surmised that if two, tethered-alkynes were employed instead, double insertion of the alkynes between the C(sp²)-C(sp³) bond could occur, resulting in the formation of eight-membered N-containing heterocyclic products (eq 1). Medium-sized heterocycles are prevalent in numerous bioactive molecules.^[7] Unfortunately, the synthesis of eight-membered rings poses a serious challenge due to disfavored enthalpic and entropic factors.^[8–10] It is also important to note that, in contrast to cyclobutanone (a class of compounds utilized by Murakami),^[11,12] heteroatom-substituted cyclobutanones are prone to polymerization and decomposition.^[13] Furthermore, self-condensation proceeds under neutral as well as basic conditions. Despite these challenges, we successfully developed a Ni/IPr catalyst that effectively couples diynes and azetidinones to afford azocines in excellent yields.^[14] This strategy not only provides medium-sized eight-membered heterocycles that are normally challenging to prepare but also represents a remarkable model system for the cleavage of C(sp²)-C(sp³) bond at low temperature.

(2)

At the onset, we reasoned that self-condensation of the azetidinone could be minimized through the use of suitable protecting groups on 'N' of 3-azetidinones. The commercially available 3-Boc-protected azetidinone (**2a**), a substrate that we found to successfully react with alkynes, and malonate diyne **1a** were chosen as a model reaction. Given our success in coupling azetidinones and alkynes with catalytic Ni/PPh₃ in toluene, we initially evaluated these conditions with **1a** and **2a** (eq 2, Table 1, entry 1). Although moderate conversion of azetidinone **2a** was observed, no desired product was detected. Other phosphine ligands were also evaluated (entries 2–8), but, again, little to no desired product was obtained in most cases. Notably, the three cases where some desired product was formed was when electron-donating phosphines were used (i.e., P(*n*-Bu)₃, PCy₃, and P(Cyp)₃, entries 5–7 respectively). A typical side reaction that plagues many cycloaddition reactions is the oligomerization of alkyne units to give aromatic products.^[15] Fearing this side reaction may be the cause of the low yields we were observing, we evaluated the Ni/PCy₃ catalyzed reaction employing slow addition of the diyne (entry 6). Unfortunately, low yield of product **3aa** was still observed. Disappointed by the poor performance of Ni/phosphine complexes, we turned our attention to highly sigma-donating, the N-heterocyclic carbene (NHC) ligand, IPr since we have had previous success in utilizing this catalyst combination in the cycloaddition of diyne (and enynes) and carbonyls (aldehydes and ketones) (entry 9).^[16] In addition, Murakami and coworkers used a Ni/IPr catalyst system to facilitate the cycloaddition of diynes and cyclobutanones.^[11] Gratifyingly, the use of IPr proved to be advantageous as product **3aa** was formed at rt in 70% yield.

Since slow addition of the diyne did not seem to result in improved yields (*vide supra*), we surmised that the β -carbon elimination step might be sluggish. Thus, to further facilitate this step, we initially evaluated reactions run at higher temperature (Table 2). Unfortunately, increased reaction temperatures proved to be deleterious to the coupling reaction and resulted in increased alkyne oligomerization. Specifically, the reaction performed at 60 °C

and 100 °C afforded azocine product in 35% and 21% yields respectively (entries 2–3). These results suggested that lowering the temperature, rather than increasing the temperature, would result in higher product yield. Indeed, to our delight, the yield of **3aa** improved significantly when the reaction temperature was lowered to 0 °C (entry 4).^[17] Running the reaction under dilute conditions led to further improvement of the yield (entry 6 vs 4 and 5). In the light of previous C-C cleavage reactions which proceed at higher temperatures, these results are highly exceptional where C-C cleavage event proceeds at 0 °C.^[18]

Other protecting groups on “N” of 3-azetidinone were also evaluated (eq 3). The use of methoxycarbonyl resulted in lower yield than Boc-protected azetidinone (**2b** vs **2a**). Alternatively, the use tosyl (Ts) group (**2c**) afforded the product in poor yield. However, the use of benzhydryl (Bnh) (**2d**) group led to an excellent yield (92%) of eight-membered azocine, **3ad**.

(3)

The substrate scope of this reaction was investigated with various diynes (Figure 1). The dioxolone moiety was well tolerated under these conditions, and the azocine product **3bd** was obtained in good yield. Not surprisingly, ethers are compatible functional groups with this chemistry (**3cd**, **3dd**).^[19] Notably, sulfonamide diyne, a substrate that is not always well tolerated in Ni-catalyzed cycloaddition chemistry, reacted with azetidinone to provide excellent yield of pyrrolidiny-azocine (**3ed**) respectively.^[20] In comparison to the ester-bearing diyne (**1a**), a diyne bearing a sulfonyl group (**1f**) afforded azocine (**3fd**) in slightly lower yield. Interestingly, ketones and nitriles, which are functional groups that also undergo cycloaddition chemistry with diynes, do not interfere with coupling with the azetidinone (**3gd**, **3hd**).^[11,20c,20e] The reaction does not rely on the presence of Thorpe-Ingold effect as all-carbon backbone diyne reacted to afford azocine (**3id**) in good yield. The incompatible nature of ester-bearing substrates in biological-active compounds prompted us to evaluate other substrates. Inspired by Carrier's recent work, oxetanyl and azetidiny diynes (**1j** and **1k**) were prepared and subjected to our optimized reaction conditions.^[21] Gratifyingly, good to excellent yield of the azocine product with a spirocyclic backbone (**3jd** and **3kd**) was observed.

The Ni/IPr-catalyzed cycloaddition strategy was also successfully applied to 3-oxacyclobutanone **2e**. Oxocine **3ae** was obtained in good yield when 3-oxetanone (**2e**) and diyne (**1a**) were subjected to standard reaction conditions (eq 4).

(4)

To address the question of regioselectivity in case of an unsymmetrical diyne, the diyne **1l** consisting methyl and hydrogen group on the terminal was subjected to standard optimized reaction conditions (eq 5). Selective formation of one regioisomer (**3ld**) was observed. An alternative unsymmetrical diyne, **1m**, whose termini differ electronically rather than sterically, was also evaluated. Again, selective formation of one regioisomer (**3md**) was observed.

Interestingly, when diynes **1n** and **1o**, which were expected to afford 6,8-fused azocine ring products, were evaluated, the expected products arising from $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$ cleavage were not obtained. Instead, spirocyclic pyran products (**3nd** and **3od**) were formed in good yields (eq 6).^[16]

(5)

(6)

A proposed mechanism for cycloaddition is shown in Scheme 1. Typically, cycloaddition begins with oxidative coupling between an alkyne and the carbonyl group.^[11,22,23] In this case, oxidative coupling would afford a spirocyclic intermediate **[M₁]**. Subsequent insertion of the pendant alkyne yields intermediate **[M₂]**, which can then either undergo reductive elimination (to afford products such as **3nd** and **3od**) or β -carbon elimination to afford metallacycle **[M₃]**. Finally, C-C bond-forming reductive elimination occurs to give azocine products as well as regenerate the catalyst. In the cycloaddition of unsymmetrical diyne **1l**, the regioselectivity is governed by the difference in the size of the substituents on the alkynes. That is, oxidative coupling between the alkyne bearing the larger group occurs first

to minimize steric interactions between the group and the ligand. Indeed, this type of regioselectivity has been observed in various cycloaddition reactions catalyzed by nickel complexes. However, in the cycloaddition of unsymmetrical diyne **1m**, the electronic nature of the alkyne, rather than the sterics, dictate the observed regioselectivity. That is, oxidative coupling of the alkyne where A= Me is more favored than with the alkyne with perturbed electronics (i.e., B= OEt). This type of electronically driven regioselectivity has not been exploited extensively in cycloaddition chemistry.^[24]

In conclusion, we have demonstrated that eight membered heterocycles can be easily accessed through Ni/IPr-catalyzed coupling of 3-azetidinone (or 3-oxetanone) and diynes. The decomposition problem associated with these constrained heterocycles was successfully addressed by the use of a proper set of reaction conditions. This method involves an interesting C-C bond cleavage which operates smoothly at 0 °C. Further synthetic and mechanistic analysis of this reaction is currently underway in our laboratory.

Experimental Section

Representative Procedure: In nitrogen filled glove box, the scintillation vial equipped with a magnetic stir bar, was charged with azetidinone (1 equiv, 0.05 M) and diyne (1.2 equiv). To this mixture in toluene was added catalyst solution (at room temperature) which was prepared in toluene by mixing Ni(cod)₂ and IPr in 1:2 molar ratio (The catalyst stock solution was allowed to stir for at least 6 h prior to use). The reaction was *immediately* brought outside of the glove box, sealed and stirred at 0 °C for 8 h. The solvent was removed under vacuum and the product was purified by silica gel flash column chromatography.

Further experimental details are available in the Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Yeung CS, Dong VM. Chem. Rev. 2011; 111:1215. [PubMed: 21391561] b) Kumar P, Louie J. Angew. Chem. Int. Ed. 2011; 50:10768.c) Chen K, Baran PS. Nature. 2009; 459:824. [PubMed: 19440196] d) Li C-J, Trost BM. Proc. Natl. Acad. Sci. USA. 2008; 105:13197. [PubMed: 18768813] e) Corbet J-P, Mignani G. Chem. Rev. 2006; 106:2651. [PubMed: 16836296]
2. For discussion on the challenges involved in C-C activation, see: Murakami M, Ito Y. Top. Organomet. Chem. 1999; 3:97. Rybtchinski B, Milstein D. Angew. Chem. Int. Ed. 1999; 38:870. Jun C-H. Chem. Soc. Rev. 2004; 33:610. [PubMed: 15592626] Miura M, Satoh T. Top. Organomet. Chem. 2005; 14:1. Murakami M. Chem. Rec. 2010; 10:326. [PubMed: 20872617] Murakami M, Matsuda T. Chem. Comm. 2011; 47:1100. [PubMed: 20953480] Seiser T, Saget T, Tran DN, Cramer N. Angew. Chem Int. Ed. 2011; 50:7740.
3. For (Rh)-catalyzed construction of carbocycles via transition metal catalyzed activation of cyclopropanes, see Wender PA, Dyckman AJ, Husfeld CO, Kadereit D, Love JA, Rieck H. J. Am. Chem. Soc. 1999; 121:10442. Wender PA, Barzilay CM, Dyckman AJ. J. Am. Chem. Soc. 2000; 123:179. [PubMed: 11273617] Wender PA, Gamber GG, Hubbard RD, Zhang L. J. Am. Chem. Soc. 2002; 124:2876. [PubMed: 11902870] Wender PA, Haustedt LO, Lim J, Love JA, Williams TJ, Yoon J-Y. J. Am. Chem. Soc. 2006; 128:6302. [PubMed: 16683779] Wang Y, Wang J, Su J, Huang F, Jiao L, Liang Y, Yang D, Zhang S, Wender PA, Yu Z-X. J. Am. Chem. Soc. 2007; 129:10060. [PubMed: 17655302] [Ru] Trost BM, Toste FD, Shen H. J. Am. Chem. Soc. 2000; 122:2379. Trost BM, Waser J, Meyer A. J. Am. Chem. Soc. 2008; 130:16424. [PubMed: 18998641] [Ni] Zuo G, Louie J. J. Am. Chem. Soc. 2005; 127:5798. [PubMed: 15839672] Zuo G, Louie J.

- Angew. Chem., Int. Ed. 2004; 43:2277. [Ir] Chatani N, Inoue H, Morimoto T, Muto T, Murai S. S. J. Org. Chem. 2001; 66:4433.
4. Murakami M, Amii H, Ito Y. Nature. 1994; 370:540.
5. For construction of carbocycles via transition metal catalyzed activation of cyclobutanones, see: Murakami M, Ashida S. Chem. Commun. 2006:4599. Matsuda T, Makino M, Murakami M. Angew. Chem. Int. Ed. 2005; 44:4608. Liu L, Ishida N, Murakami M. Angew. Chem., Int. Ed. 2012; 51:2485. Wender PA, Correa AG, Sato Y, Sun R. R. J. Am. Chem. Soc. 2000; 122:7815. Montero-Campillo MM, Rodríguez-Otero J, Cabaleiro-Lago EM. Tetrahedron. 2008; 64:6215.
6. For Ni-catalyzed coupling of azetidinone and alkynes, see: Kumar P, Louie J. Org. Lett. 2012; 14:2026. [PubMed: 22468962] Ho KYT, Aïssa C. Chem-Eur. J. 2012; 18:3486. [PubMed: 22359347]
7. For selected biologically important azocine compounds, see: Winkler JD, Londregan AT, Hamann MT. Organic Letters. 2006; 8:2591. [PubMed: 16737321] Winkler JD, Londregan AT, Ragains JR, Hamann MT. Organic Letters. 2006; 8:3407. [PubMed: 16836417] Vedejs E, Galante RJ, Goekjian PG. J. Am. Chem. Soc. 1998; 120:3613.
8. For construction of eight membered carbocycles via transition metal catalyzed cycloaddition, see: Wender PA, Ihle NC. J. Am. Chem. Soc. 1986; 108:4678. Wender PA, Tebbe MJ. Synthesis. 1991:1089. Wender PA, Nuss JM, Smith DB, Suárez-Sobrinho A, Vågberg J, Decosta D, Bordner J. J. Org. Chem. 1997; 62:4908. Evans PA, Robinson JE, Baum EW, Fazal AN. J. Am. Chem. Soc. 2002; 124:8782. [PubMed: 12137516] Gilbertson SR, DeBoef B. J. Am. Chem. Soc. 2002; 124:8784. [PubMed: 12137517] Varela JA, Castedo L, Saa C. Org. Lett. 2003; 5:2841. [PubMed: 12889888] Evans PA, Baum EW. J. Am. Chem. Soc. 2004; 126:11150. [PubMed: 15355086] Evans PA, Baum EW, Fazal AN, Pink M. Chem. Commun. 2005:63. Lee SI, Park SY, Chung YK. Adv. Synth. Catal. 2006; 348:2531. Wender PA, Christy JP. J. Am. Chem. Soc. 2006; 128:5354. [PubMed: 16620102] DeBoef B, Counts WR, Gilbertson SR. J. Org. Chem. 2007; 72:799. [PubMed: 17253798] Hilt G, Janikowski J. Angew. Chem., Int. Ed. 2008; 47:5243.
9. a) For ring closing metathesis route to medium sized heterocycles, see Deiters A, Martin SF. Chem. Rev. 2004; 104:2199. [PubMed: 15137789] b) For Rh-catalyzed elegant access to azocines, see: Yu RT, Friedman RK, Rovis T. J. Am. Chem. Soc. 2009; 131:13250. [PubMed: 19711950]
10. Michaut A, Rodriguez J. Angew. Chem., Int. Ed. 2006; 45:5740.
11. For studies focused on carbocycles by utilizing nickel-catalyzed β -carbon elimination, see: Murakami M, Ashida S, Matsuda T. J. Am. Chem. Soc. 2005; 127:6932. [PubMed: 15884919] Murakami M, Ashida S, Matsuda T. J. Am. Chem. Soc. 2006; 128:2166. [PubMed: 16478142] Murakami M, Makino M, Ashida S, Matsuda T. Bull. Chem. Soc. Jpn. 2006; 79:1315. Ashida S, Murakami M. Bull. Chem. Soc. Jpn. 2008; 81:885.
12. For prior work with cyclobutenones, see: Liebeskind LS, Baysdon SL, South MS, Iyer S, Leeds JP. Tetrahedron. 1985; 41:5839. b) Liebeskind LS, Chidambaram R, Mitchell D, Foster B. Pure Appl. Chem. 1988; 60:2734. c) Huffman MA, Liebeskind LS. J. Am. Chem. Soc. 1991; 113:2771. d) Huffman MA, Liebeskind LS. J. Am. Chem. Soc. 1993; 115:4895. e) Liebeskind LS, Bombrun A. J. Org. Chem. 1994; 59:1149.
13. a) Dejaegher Y, Kuz'menok NM, Zvonok AM, De Kimpe N. Chem. Rev. 2001; 102:29. [PubMed: 11782128] b) De Smaele D, Dejaegher Y, Duvey G, De Kimpe N. Tetrahedron Lett. 2001; 42:2373.
14. This synthetic technology was patented by us in Aug. 2011 (P. Kumar, J. Louie, U#5170)
15. Wender PA, Christy JP. J. Am. Chem. Soc. 2007; 129:13402. [PubMed: 17929819]
16. For Ni-catalyzed cycloaddition of diynes and enynes with carbonyls, see: Tekavec TN, Louie J. Org. Lett. 2005; 7:4037. [PubMed: 16119961] Tekavec TN, Louie J. J. Org. Chem. 2008; 73:2641. [PubMed: 18318544]
17. When PCy₃ was used as a ligand in reaction conducted at 60 °C and rt, yields of **1a** were 47 % and 24 %, respectively.
18. Nakao Y, Hiyama T. Pure Appl. Chem. 2008; 80:1097.
19. The structure of **3dd** was unambiguously determined by single crystal X-ray crystallography (see Supporting Information).

20. A diyne containing an NTs group in the backbone is either ineffective or less effective coupling partner in nickel-catalyzed cycloaddition chemistry, see: Louie J, Gibby JE, Farnworth MV, Tekavec TN. *J. Am. Chem. Soc.* 2002; 124:15188. [PubMed: 12487590] Tekavec TN, Arif AM, Louie J. *Tetrahedron*. 2004; 60:7431. McCormick MM, Duong HA, Zuo G, Louie GJ. *J. Am. Chem. Soc.* 2005; 127:5030. [PubMed: 15810832] Kumar P, Troast DM, Cella R, Louie J. *J. Am. Chem. Soc.* 2011; 133:7719. [PubMed: 21528904] Kumar P, Prescher S, Louie J. *Angew. Chem. Int. Ed.* 2011; 50:10694.
21. Burkhard JA, Wuitschik G, Rogers-Evans M, Müller K, Carreira EM. *Angew. Chem. Int. Ed.* 2010; 49:9052.
22. a) Miller KM, Huang W-S, Jamison TF. *J. Am. Chem. Soc.* 2003; 125:3442. [PubMed: 12643701] b) Montgomery J, Sormunen GJ. *Top. Curr. Chem.* 2007; 279:1. c) Malik HA, Sormunen GJ, Montgomery J. *J. Am. Chem. Soc.* 2010; 132:5966. [PubMed: 20384301] d) McCarren PR, Liu P, Cheong PH-Y, Jamison TF, Houk KN. *J. Am. Chem. Soc.* 2009; 131:6654. [PubMed: 19397371] e) Liu P, McCarren P, Cheong PH-Y, Jamison TF, Houk KN. *J. Am. Chem. Soc.* 2010; 132:2050. [PubMed: 20095609]
23. Based on the recent DFT calculations, the possibility of initial oxidative coupling of two alkyne units cannot be ruled out completely Tao J-Y, Fang D-C, Chass GA. *Phys. Chem. Chem. Phys.* 2012; 14:6937.
24. a) McDonald FE, Zhu HYH, Holmquist CR. *J. Am. Chem. Soc.* 1995; 117:6605. b) Castro J, Sorensen H, Riera A, Morin C, Moyano A, Pericas MA, Greene AE. *J. Am. Chem. Soc.* 1990; 112:9388. c) Hanazawa T, Sasaki K, Takayama Y, Sato F. *J. Org. Chem.* 2003; 68:4980. [PubMed: 12790616] d) Komine Y, Kamisawa A, Tanaka K. *Org. Lett.* 2009; 11:2361. [PubMed: 19473045]

Figure 1. Ni-catalyzed cycloaddition of diynes (**1b-1k**) and azetidinones (**2d**)[a][a] Azetidinone **2d** (0.1 M), diyne **1b-1k** (0.12 M), 10 mol % Ni(cod)₂, 20 mol % IPr, toluene, 8h.

Scheme 1.
 Proposed mechanism of cycloaddition

Table 1Ligand evaluation for the Ni-catalyzed coupling of diyne **1a** and azetidinone **2a**^[a]

entry	ligand	2a conversion ^[b]	3aa isolated yield
1	PPh ₃	49%	n.d. ^[c]
2	DPPF	48%	n.d. ^[c]
3	BINAP	-	n.d. ^[c]
4	PCy ₂ Ph	60%	n.d. ^[c]
5	P(<i>n</i> -Bu) ₃	72%	23%
6	PCy ₃	83%	37% (28%) ^[d]
7	P(Cyp) ₃	81%	30%
8		18%	n.d. ^[c]
9	IPr	>99%	70% ^[e]

^[a] Azetidinone **2a** (0.1 M), diyne **1a** (0.12 M), 10 mol % Ni(cod)₂, L (20 mol % for entry 1, 4–8 and 10 mol % for entries 2–3), toluene, 100 °C, 12h.

^[b] Conversion of diyne was determined by ¹H NMR sing 1,3,5-trimethoxybenzene as an internal standard.

^[c] n.d. = not detected.

^[d] Diyne **1a** was added dropwise to the reaction mixture.

^[e] Reaction was run at rt.

Table 2Temperature effect evaluation on the Ni/IPr-catalyzed coupling of **1a** and **2a** to afford **3aa**^[a]

entry	temperature	a concentration	1a isolated yield
1	rt	0.1 M	70%
2	60 °C	0.1 M	35%
3	100 °C	0.1 M	21%
4	0 °C	0.1 M	84%
5	0 °C	0.2 M	68%
6	0 °C	0.05 M	88%

^a Azetidinone **2a** (0.1 M), diyne **1a** (0.12 M), 10 mol % Ni(cod)₂, 20 mol % IPr, toluene, 8h.