HETEROCYCLES, Vol 22, No 4, 1984

# HETEROCYCLIC SYNTHESIS BY METAL CARBONYL INDUCED CYCLIZATION REACTION

Yoshiki Ohshiro* and Toshikazu Hirao
Department of Applied Chemistry, Faculty of Engineering, Osaka
University, 2-1 Yamada-oka, Suita, Osaka 565, Japan

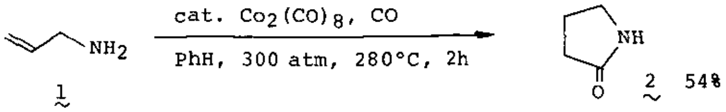
Abstract - Metal carbonyl induced cyclization reactions provide useful methods for heterocyclic synthesis. This review surveys their recent progress.

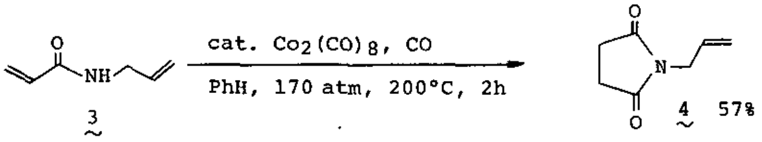
## 1. Introduction

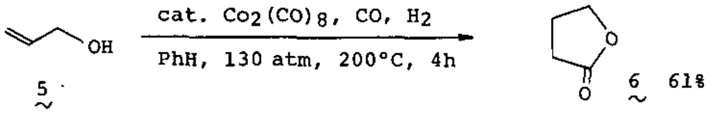
Recently, organic synthesis with transition metal compounds has been developing to give versatile methods for a variety of highly selective transformations. The application of this methodology to heterocyclic synthesis constitutes a new area. The metal as transition metal carbonyls is generally present in low oxidation state, so metal carbonyls react as nucleophiles or electron transfer agents. Another important characteristic of metal carbonyls is carbonylation reactions based on the insertion of carbon monoxide. From these points of view, transition metal carbonyls play an important role in organic synthesis. This review describes heterocyclic syntheses by metal carbonyl induced cyclization reactions.

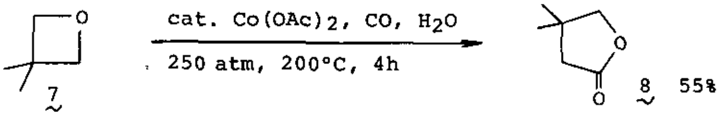
## 2. Heterocyclic Synthesis by Carbonylation

Carbonylation reactions by metal carbonyls have been invesitigated in detail as exemplified in oxo and Reppe reactions. Allylamine (1) and the acrylamide 3 undergo the $Co_2(CO)_8$-catalyzed cyclization into the lactam 2 or the cyclic imide 4, respectively.[1] The same procedure is extended to the lactone ring formation from allylalcohol (5).[2] Another route to lactones has been explored by the insertion of carbon monoxide into the oxetane 7 or tetrahydrofuran with $Co_2(CO)_8$.[3]

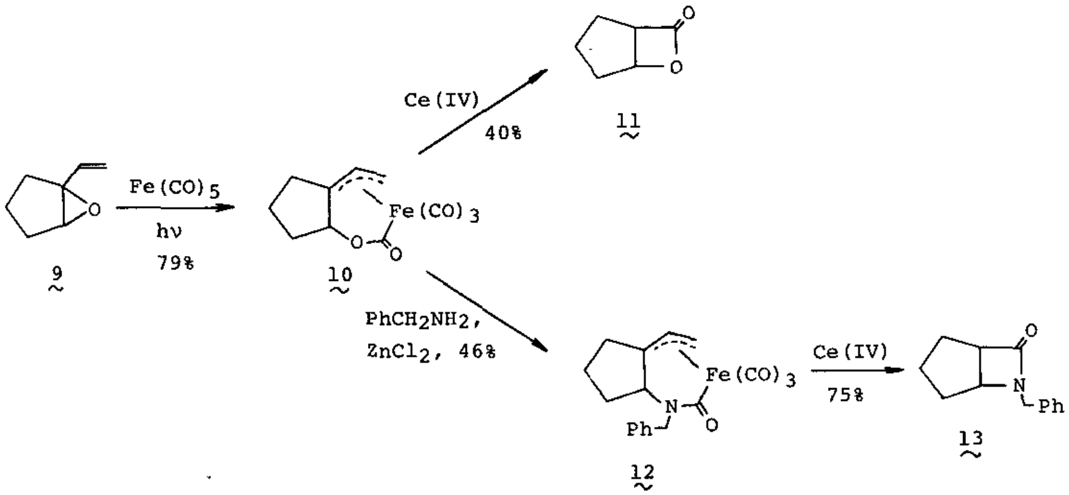




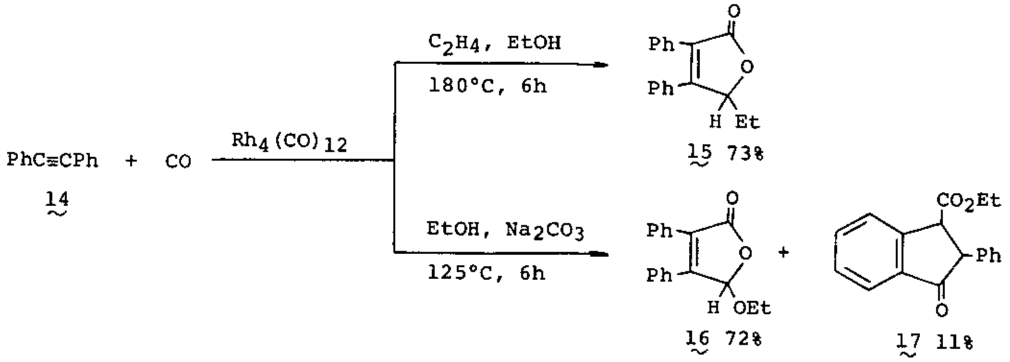




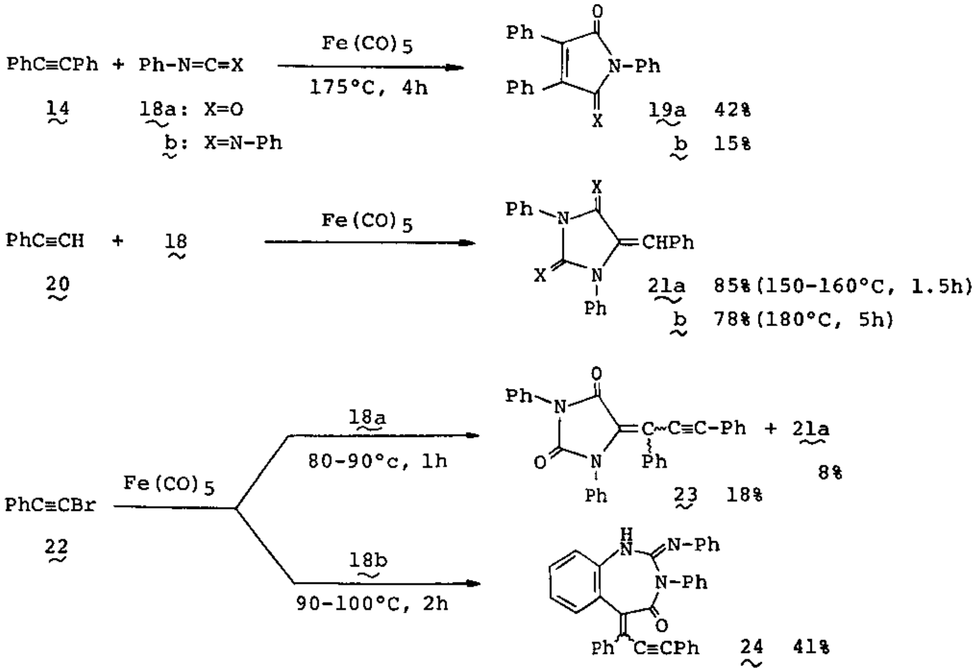
Photolysis of the vinyl oxirane 9 in the presence of $Fe(CO)_5$ allows ring opening into the iron complex intermediate 10, which is convered to the lactone 11 on oxidation with Ce(IV).[4] Treatment of the iron complex intermediate 10 with benzylamine and $ZnCl_2$ followed by oxidation leads to the β-lactam 13.[5]



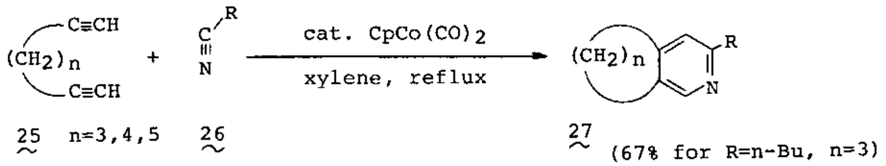
Hydrocarbonylation of acetylenes with ethylene is catalyzed by $Rh_4(CO)_{12}$ in ethanol to give 5-ethyl-2(5H)-furanones such as 15.[6] In the absence of ethylene, ethanol is intoduced to the product 16.[7]

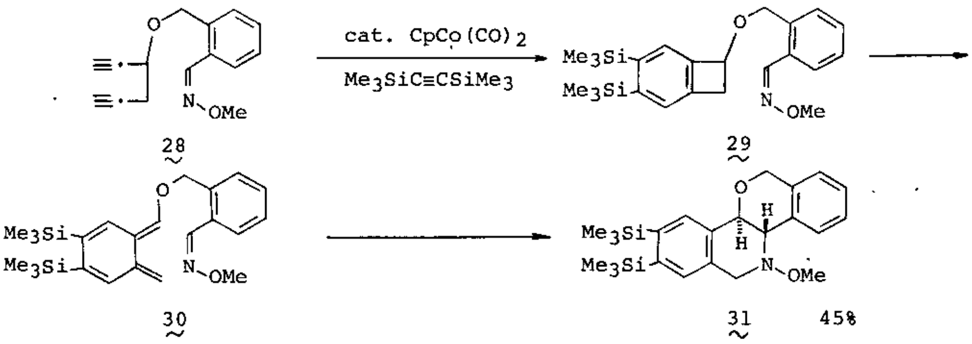


Diphenylacetylene (14) is subjected to the $Fe(CO)_5$-induced cyclization reaction with phenyl isocyanate (18a) or N,N'-diphenylcarbodiimide (18b) to form the five-membered heterocyle 19a or 19b, respectively, with incorporation of carbon monoxide.[8] On the similar treatment of phenylacetylene (20), however, the insertion of carbon monoxide is not observed, giving the 1:2 adduct 21.[9] The reaction of bromophenylacetylene (22) proceeds in the different way, depending on the heterocumulenes.[10]

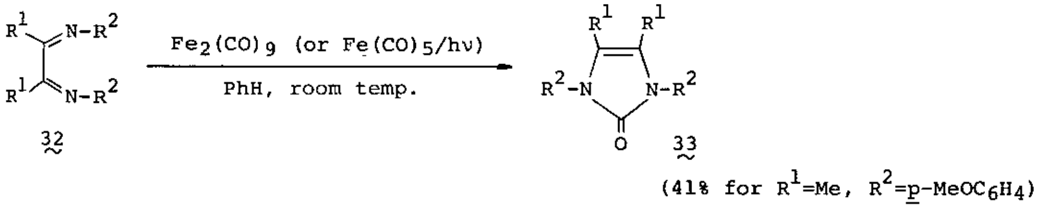


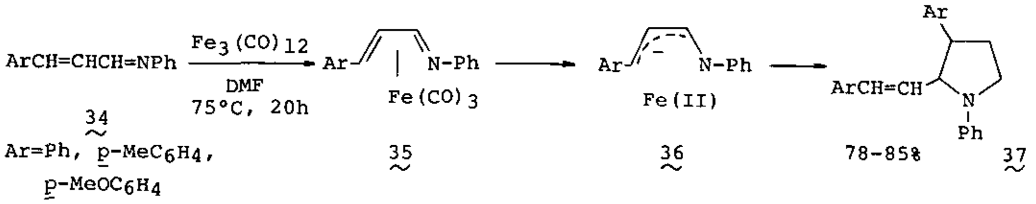
Formation of pyridine rings is achieved by the $CpCo(CO)_2$-catalyzed reaction of the diacetylenic compound **25** with the nitrile **26**.[11] This process seems to involve cobaltacyclopentadiene complex intermediates.[12] This methodology is extended to the synthesis of pyridone derivatives from isocyanates or carbodiimides.[13] Cycloaddition of the 1,5-hexadiene derivative **28** with bis(trimethylsilyl)acetylene gives the benzocyclobutene **29**, which is the *o*-quinodimethane precursor **30** capable of being trapped by the imino ether moiety to produce **31**.[14]



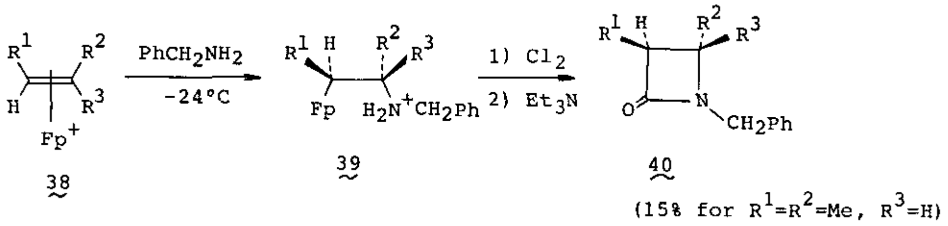


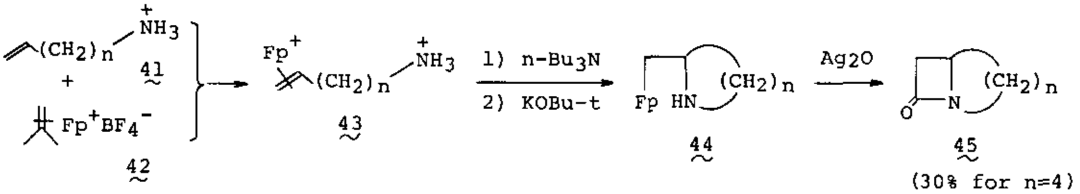
The 1,4-diaza-1,3-diene **32** is cyclized to the five-membered heterocycle **33** on treatment with $Fe_2(CO)_9$ or $Fe(CO)_5$ under ultraviolet irradiation (Photolysis of $Fe(CO)_5$ in acetic acid is known to give $Fe_2(CO)_9$.[15]).[16] Unlike the case of **32**, the 1-aza-1,3-diene **34** is converted to the pyrrolidine **37**.[17] The reaction path is explained by the [2+3] cycloaddition of **34** with the allyl anion intermediate **36** derived from the complex **35**.

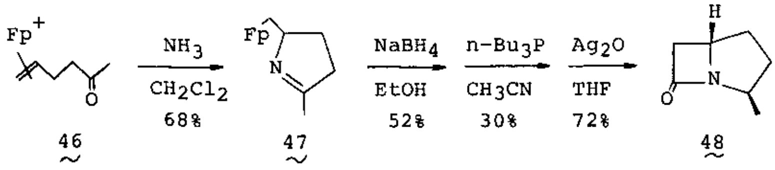




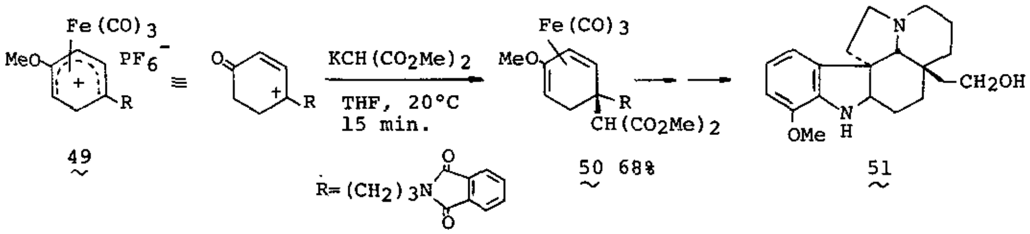
Activation of olefins towards nucleophiles has been performed by the use of Fp(olefin)cation complex (38, Fp=CpFe$(CO)_2$). Addition of benzylamine to Fp(olefin)cation complex and oxidation result in the stereospecific ring closure accompanied by the insertion of carbon monoxide, leading to the β-lactam 40.[18] The cation complex 43 which is obtained by the exchange of Fp(isobutene) tetrafluoroborate (42) with the corresponding olefinic ammonium salt 41 undergoes the intramolecular cyclization to the fused β-lactam 45. Attack of ammonia to the cation complex 46 derived from 5-hexen-2-one gives the pyrroline complex 47, which is reduced and cyclized to the β-lactam 48.[19]



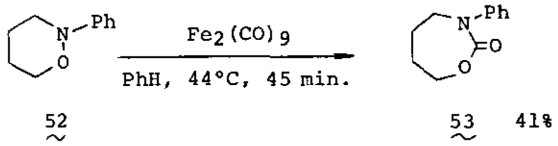


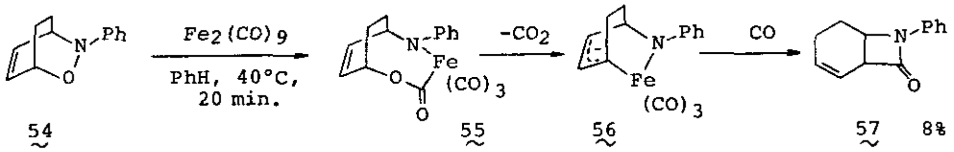


The different type of iron cation complex, tricarbonylcyclohexadienyliumiron complex, is regarded as a cyclohexenone γ-cation equivalent. For example, 49 undergoes the regioselective nucleophilic attack to give 50, which is a key intermediate for the preparation of (±)-limaspermine (51).[20]

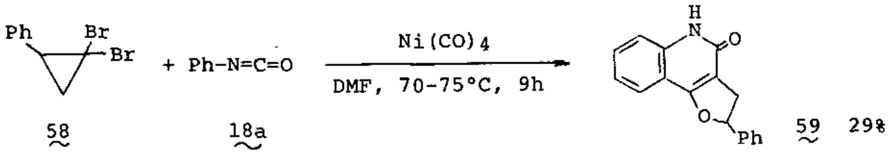


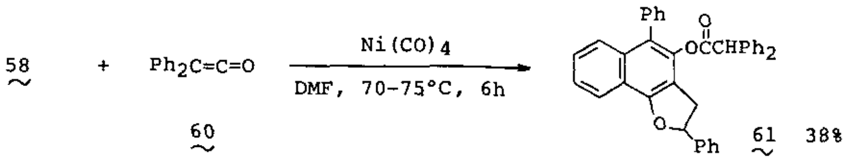
The insertion of carbon monoxide to the tetrahydrooxazine 52 is induced by $Fe_2(CO)_9$.[21] In the case of the fused oxazine 54, the construction of the β-lactam ring is performed by carbonylation and decarboxylation reactions.[22]



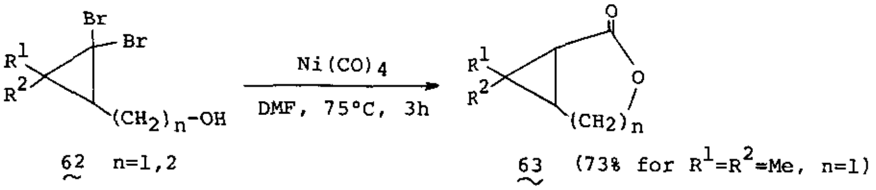


1,1-Dibromo-2-phenylcyclopropane (58) is subjected to ring opening with $Ni(CO)_4$ in the presence of phenyl isocyanate to yield the furoquinoline 59. Similarly, the naphthofuran 61 is formed from diphenylketene (60). Carbon monoxide is introduced as an ether linkage in both cases.[23]

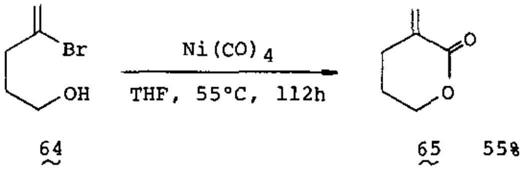




The presence of a hydroxyl group in gem-dibromocyclopropanes allows the $Ni(CO)_4$-induced intramolecular reductive carbonylation of 62 into the bicyclic lactones 63.[24] This method provides a facile synthesis for the precursor of cis-chrysanthemic acid.

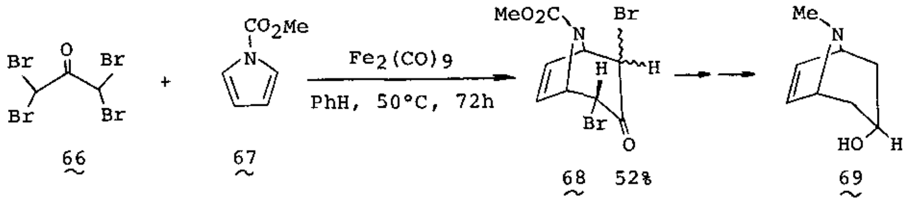


The intramolecular carbonylation of the bromoolefin 64 is realized by $Ni(CO)_4$ to give the α-methylene lactone 65.[25] Initial attack of the hydroxyl oxygen to $Ni(CO)_4$ is presumably involved in these transformations.

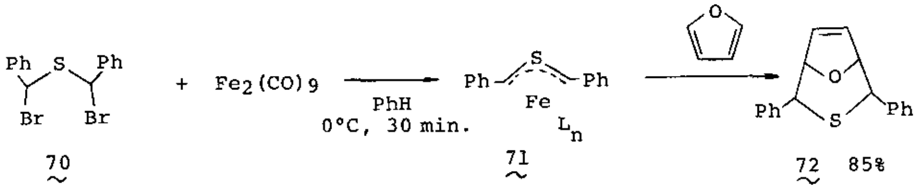


### 3. Heterocyclic Synthesis by Dehalogenation

Generally, organic halides are not so reactive towards metal carbonyls. Activated organic halides are allowed to undergo direct dehalogenation with metal carbonyls. α,α'-Dibromoketones are treated with $Fe_2(CO)_9$ to generate oxyallyl complexes. These complexes are revealed to be versatile intermediates which are able to react with olefinic compounds. Based on the reaction of α,α,α',α'-tetrabromoacetone (66) with N-carbomethoxypyrrole (67), tropane alkaloid is synthesized selectively.[26]

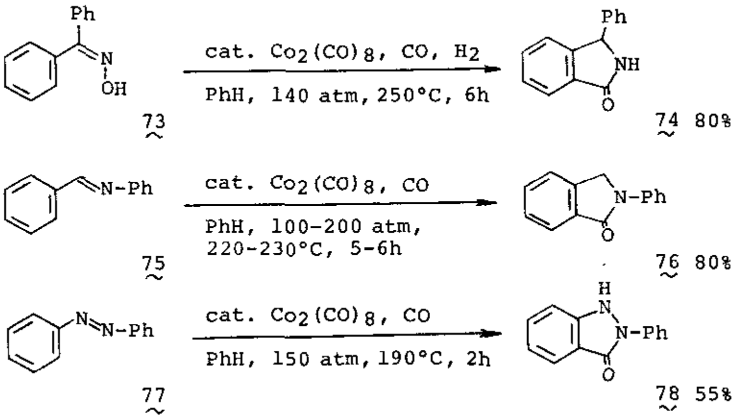


Bis(α-bromobenzyl)sulfide (70) forms the stable ylide complex 71 upon treatment with $Fe_2(CO)_9$. The addition of furan to 71 yields the heterocycle 72.[27] The use of the corresponding sulfoxide instead of the sulfide 70 leads to the same product, probably due to deoxygenation of the sulfoxide function with $Fe_2(CO)_9$.

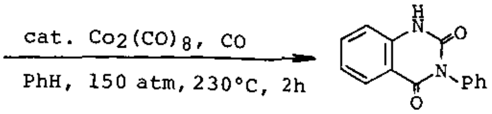


### 4. Heterocyclic Synthesis by Ortho-Metallation

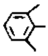
Ortho-metallation takes place if a functional group is present in a suitable position for coordination. This metallation provides useful synthetic routes to heterocycles. They are illustrated in the $Co_2(CO)_8$-catalyzed heterocyclic synthesis from oxime,[28] Schiff base,[29] and azo derivatives.[30]

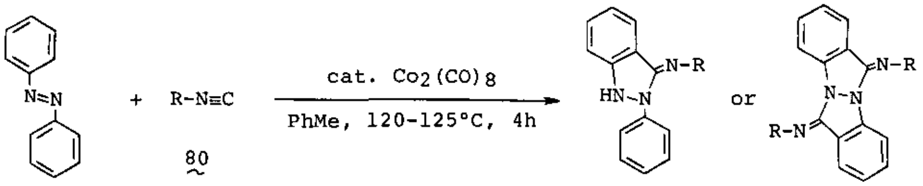


77



79 80%

Isonitriles are introduced by the similar cyclization reactions of azobenzene (77) as shown in the following scheme.[31] Ortho-metallation in both aromatic rings is observed depending upon the substituent of isonitriles. The use of the isonitrile complex ($Co_2$(  -N≡C)$_8$) gives the same product 82.[32]



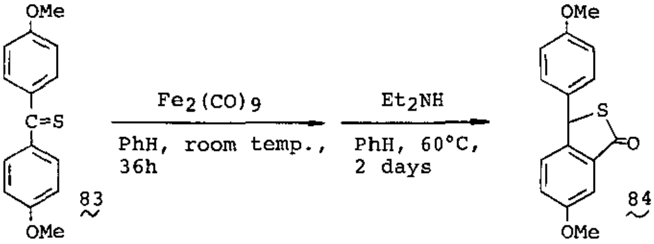
80

77

81
R=Ph, 53%

82
R=2,6-$Me_2C_6H_3$, 36%

The isobenzothiophene 84 is formed in the reaction of the thioketone 83 with $Fe_2(CO)_9$ followed by treatment with diethylamine.[33]

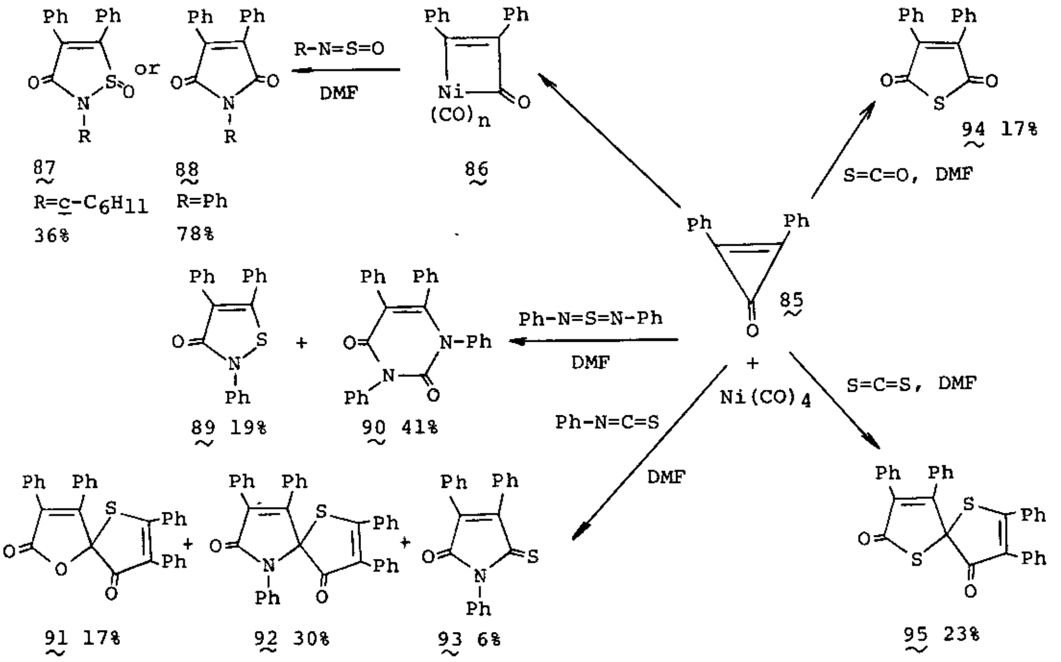


83

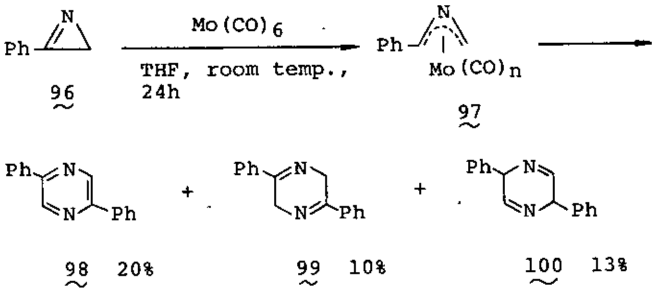
84 49%

## 5. Heterocyclic Synthesis by Ring Enlargement of Three-Membered Ring Compounds

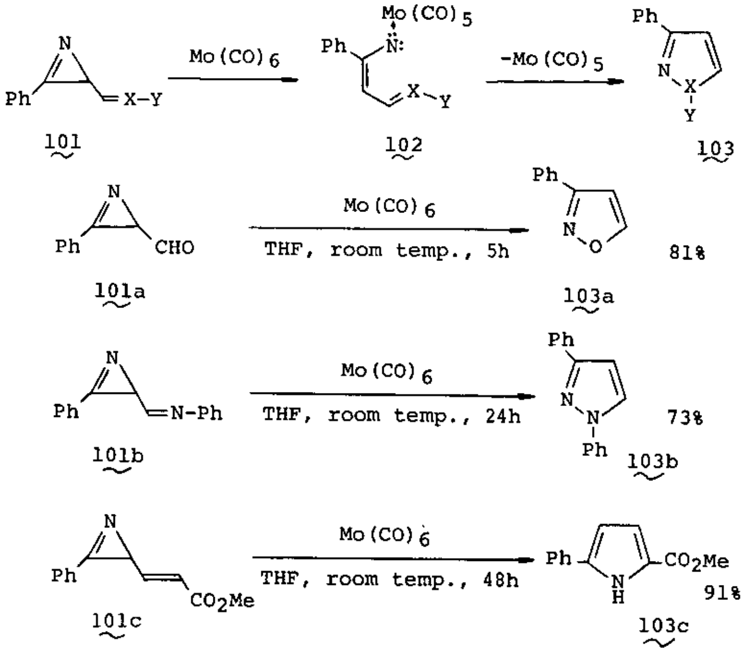
The ring cleavage of diphenylcyclopropenone (85) with $Ni(CO)_4$ provides a new approach to heterocycles. The cycloaddition of diphenylcyclopropenone to N-sulfinylamines gives the heterocycle 87 or 88, depending on the substituent of N-sulfinylamines.[34] The nickelacyclobutenone complex 86 is considered to be an intermediate in this transformation.[35] Starting from N,N'-diphenyl sulfur diimide, the six-membered heterocycle 89 is formed as a main product, being accompanied by the exchange of sulfur with the carbonyl group.[36] It should be noted that the spiro compound 92 derived by the cycloaddition to both double bonds of phenyl isothiocyanate is obtained. In contrast to the reaction with carbonyl sulfide, the selective formation of the spiro compound 95 from carbon disulfide is observed.



Ring enlargement of azirines is readily achieved by metal carbonyls. On treatment with $Mo(CO)_6$, the azirine 96 is converted to its dimers via the intermediate 97. The dimerization proceeds similarly in the presence of $Cr(CO)_6$ or $W(CO)_6$ to give 98 and 100.[37] $[CpFe(CO)_2]_2$ also promotes the dimerization of 96 to 98.[38]



Azirines having formyl, imino, or vinyl groups undergo the $Mo(CO)_6$-induced intramolecular cyclization to heterocyclic compounds.[39] The complex 102 is assumed to be involved as an intermediate.



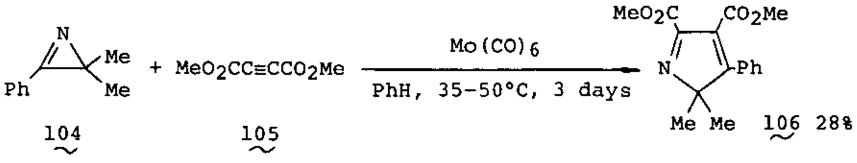
101 102 103

101a → 103a 81%

101b → 103b 73%

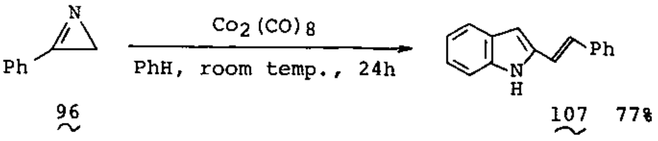
101c → 103c 91%

Addition of dimethyl acetylenecarboxylate (105) to the azirine 104 gives the pyrrole 106.[40]



104 105 106 28%

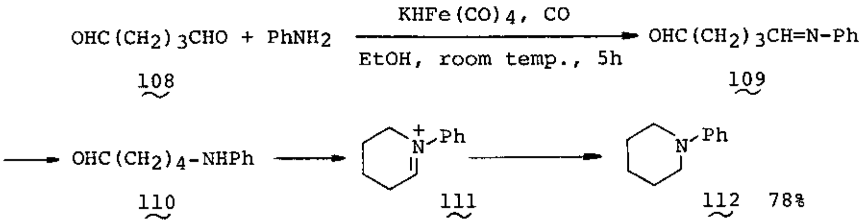
The indole derivative 107 is formed in the reaction of 96 with $Co_2(CO)_8$[41] or $[Rh(CO)_2Cl]_2$.[42]

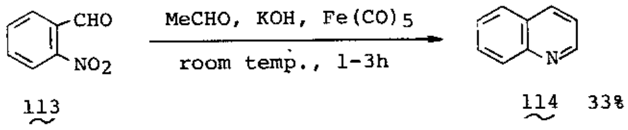


96 107 77%

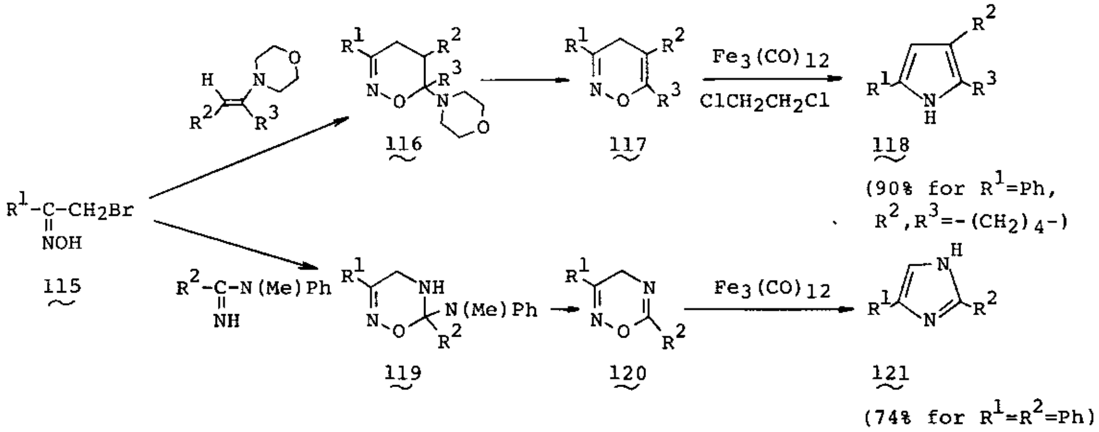
## 6. Heterocyclic Synthesis by Reduction with Iron Carbonyl Complex

Ferrate complexes such as $M_2Fe(CO)_4$[43] and $MHFe(CO)_4$ (M=Na, K) are versatile reagents as exemplified in alkylation of amines or ammonia with aldehydes. The use of glutaraldehyde (**108**) leads to the formation of the piperizine ring **112**.[44] The reaction is explained by the intermediacy of the Schiff base **109** and the immonium salt **111**, followed by reduction. Reduction of a nitro group is achieved by the ferrate complex, which is applied to the quinoline synthesis.[45]





The following examples are also representative of deoxygenation with $Fe_3(CO)_{12}$ to give the heterocycles **118** and **121**.[46]



## 7. Conclusion

We have described typical examples of heterocyclic syntheses induced by metal carbonyls. Metal carbonyls are quite useful reagents for the elaboration of complicated rings which are not so easily accessible. More facile and versatile routes for highly selective design of heterocycles will be developed by transition metal induced new reactions.[47]

## REFERENCES

1. J. Falbe and F. Korte, *Chem. Ber.*, 1965, **98**, 1928.
2. A. Matsuda, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 1876.
3. H. J. Nienburg and G. Elchnigg, Ger. Pat. 1066572 (1959); *Chem. Abstr.*, 1961, **55**, 10323.
4. G. D. Annis and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 1977, 581; G. D. Annis, S. V. Ley, and R. Sivaramakrishnan, *J. Organometal. Chem.*, 1979, **182**, C11.
5. G. D. Annis, E. M. Hebbethwaite, and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 1980, 297.
6. P. Hong, T. Mise, and H. Yamazaki, *Chem. Lett.*, 1981, 989.
7. T. Mise, P. Hong, and H. Yamazaki, *J. Org. Chem.*, 1983, **48**, 238.
8. K. Kinugasa and T. Agawa, *Organometal. Chem. Syn.*, 1972, **1**, 427; *J. Organometal. Chem.*, 1973, **51**, 329.
9. Y. Ohshiro, K. Kinugasa, T. Minami, and T. Agawa, *J. Org. Chem.*, 1970, **35**, 2136.
10. A. Baba, Y. Ohshiro, and T. Agawa, *J. Organometal. Chem.*, 1975, **87**, 247.
11. A. Naiman and K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, 1977, **16**, 708.
12. Y. Wakatsuki and H. Yamazaki, *Tetrahedron Lett.*, 1973, 3383; *Synthesis*, 1976, 26; H. Bönnemann, R. Brinkmann, and H. Schenkluhn, *ibid.*, 1974, 575; H. Bönnemann and R. Brinkmann, *ibid.*, 1975, 600; D. Tatone, T. C. Dich, R. Nacco, and C. Botteghi, *J. Org. Chem.*, 1975, **40**, 2987.
13. P. Hong and H. Yamazaki, *Tetrahedron Lett.*, 1977, 1333; *Synthesis*, 1977, 50.
14. R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1976, **98**, 6755.
15. R. B. King, "Organometallic Syntheses," Vol. 1, p. 93, Academic Press (1965).
16. H.-W. Frühauf, A. Landers, R. Goddard, and C. Kruger, *Angew. Chem. Int. Ed. Engl.*, 1978, **17**, 64.

17. Y. Otsuji, *J. Synth. Org. Chem. Jpn.*, 1980, **38**, 1216.

18. P. K. Wong, M. Madhavarao, D. F. Marten, and M. Rosenblum, *J. Am. Chem. Soc.*, 1977, **99**, 2823.

19. S. R. Berryhill and M. Rosenblum, *J. Org. Chem.*, 1980, **45**, 1984; S. R. Berryhill, T. Price, and M. Rosenblum, *ibid.*, 1983, **48**, 158.

20. A. J. Pearson and D. C. Rees, *J. Am. Chem. Soc.*, 1982, **104**, 1118.

21. Y. Becker, A. Eisenstadt, and Y. Shvo, *Tetrahedron*, 1974, **30**, 839.

22. Y. Becker, A. Eisenstadt, and Y. Shvo, *Tetrahedron*, 1978, **34**, 799; *J. Organometal. Chem.*, 1978, **155**, 63.

23. Y. Ohshiro, K. Kimura, and T. Agawa, unpublished.

24. T. Hirao, Y. Harano, Y. Yamana, Y. Ohshiro, and T. Agawa, *Tetrahedron Lett.*, 1983, **24**, 1255.

25. M. F. Semmelhack and S. J. Brickner, *J. Org. Chem.*, 1981, **46**, 1723.

26. R. Noyori, S. Makino, Y. Baba, and Y. Hayakawa, *Tetrahedron Lett.*, 1974, 1049; R. Noyori, Y. Baba, and Y. Hayakawa, *J. Am. Chem. Soc.*, 1974, **96**, 3336.

27. T. Koyanagi, J.-i. Hayami, and A. Kaji, *Chem. Lett.*, 1976, 971.

28. A. Rosenthal, R. F. Astbury, and A. Hubscher, *J. Org. Chem.*, 1958, **23**, 1037.

29. S. Murahashi, *J. Am. Chem. Soc.*, 1955, **77**, 6403.

30. S. Murahashi and S. Horiie, *J. Am. Chem. Soc.*, 1956, **78**, 4816.

31. Y. Yamamoto and H. Yamazaki, *J. Org. Chem.*, 1977, **42**, 4136.

32. Y. Yamamoto and H. Yamazaki, *J. Organometal. Chem.*, 1976, **137**, C31.

33. H. Alper and W. G. Root, *J. Am. Chem. Soc.*, 1975, **97**, 4251.

34. A. Baba, Y. Ohshiro, and T. Agawa, *Chem. Lett.*, 1976, 11.

35. G. Ayrey, C. W. Bird, E. M. Briggs, and A. F. Harmer, *Organometal. Chem. Syn.*, 1970/71, **1**, 187.

36. Y. Ohshiro, H. Nanimoto, A. Baba, T. Tone, H. Tanaka, M. Komatsu, and T. Agawa, *Heterocycles*, 1978, **9**, 123.

37. H. Alper and S. Wollowitz, *J. Am. Chem. Soc.*, 1975, **97**, 3541.

38. H. Alper and T. Sakakibara, *Can. J. Chem.*, 1979, **57**, 1541.

39. H. Alper, J. E. Prickett, and S. Wollowitz, *J. Am. Chem. Soc.*, 1977, **99**, 4330.

40. A. Inada, H. Heimgartner, and H. Schmid, *Tetrahedron Lett.*, 1979, 2983.

41. H. Alper and J. E. Prickett, *Tetrahedron Lett.*, 1976, 2589.

42. H. Alper and J. E. Prickett, *J. Chem. Soc., Chem. Commun.*, 1976, 483.

43. J. P. Collman, Acc. Chem. Res., 1975, **8**, 342.

44. Y. Watanabe, S. C. Shim, T.-a. Mitsudo, M. Yamashita, and Y. Takegami, Bull. Chem. Soc. Jpn., 1976, **49**, 2302; Y. Watanabe, S. C. Shim, H. Uchida, T. Mitsudo, and Y. Takegami, Tetrahedron, 1979, **35**, 1433.

45. Y. Watanabe, K. Takatsuki, S. C. Shim, T.-a. Mitsudo, and Y. Takegami, Bull. Chem. Soc. Jpn., 1978, **51**, 3397.

46. S. Nakanishi, Y. Shirai, K. Takahashi, and Y. Otsuji, Chem. Lett., 1981, 869; S. Nakanishi, J. Nantaku, and Y. Otsuji, ibid., 1983, 341.

47. J. L. Davidson and P. N. Preston, "Advances in Heterocyclic Chemistry," Academic Press, 1982, Vol. 30, p. 321.

Received, 11th August, 1983