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## SYNTHESIS OF NITROGEN CONTAINING HETEROCYCLES BY USING CARBON-NITROGEN DOUBLE BOND

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**Abstract** – Recent achievements in the construction of mainly nitrogen containing heterocycles by the intramolecular cyclization of alkenylanilides *via* activation of unsaturated bonds are reviewed. NIS or ZnX<sub>2</sub> activation of 2-alkenylanilines and 2-alkynylanilines gave quinolines or indoles in high yields. Reaction of 2-aminobenzaldehyde with acetophenones under basic conditions gave dibenzonaphthyridines in one-pot operation. Other nitrogen and chalcogene containing heterocycles were also synthesized by the reaction of ketone hydrazones with chalcogen halides.

### CONTENTS

1. Introduction
2. Quinolines
3. Indoles
4. Benzoxazines
5. Benzothiazines
6. Dibenzonaphthyridines
7. Benzodiazepines and Isoquinolines
8. Reaction of Ketone Hydrazones with Chalcogen Derivatives
9. 1,3,4-Selenadiazolines
10. 2,5-Diarylselenophene
11. 1,3,4-Thiadiazoles
12. Wagner-Meerwein Rearrangement
13. Cyclic Polysulfides
14. Reaction of Camphor and Fenchone Hydrazone with Tellurium Tetrachloride

15. Tellurophenes

16. Conclusion

## 1. INTRODUCTION

Heteroaromatic rings are important structural elements in organic and pharmaceutical chemistry. Synthesis of indole, quinoline, benzoxazine, benzothiazine, naphthyridine and their derivatives has been of considerable interest to chemists because these heterocycles contribute to potential antibacterial, antitumoral, antimalarial, antiasthmatic, antihypertensive, anti-inflammatory, and antiplatelet properties.<sup>1-3</sup> Thus, many synthetic methods concerning to these nitrogen heterocycles were developed from 19th century, which include Fischer indole synthesis, Friedländer quinoline synthesis and many other name reactions.<sup>4</sup> Recently, transition metal-catalyzed coupling reactions provide a key role in organic synthesis. Sonogashira coupling reaction is one of the most widely used synthetic procedure for the coupling of vinyl or aryl halides with terminal alkynes to form conjugated enynes or aryl alkynes. The reaction has become an essential tool in the synthesis of heterocyclic compounds.<sup>5</sup> This review provides a simple synthesis of nitrogen, oxygen, sulfur, selenium, and tellurium containing heterocycles via intramolecular cyclization of alkenyl or alkynyl aromatic compounds with carbon nitrogen double bond via unsaturated bond activation (Figure 1).

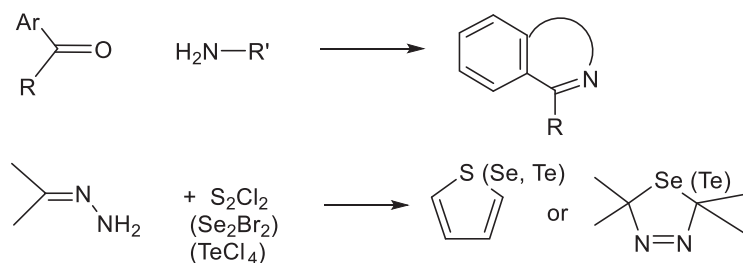
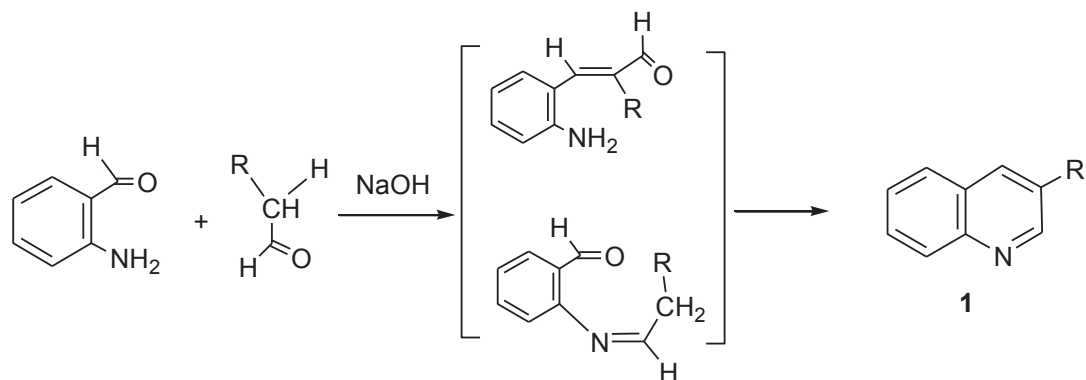


Figure 1

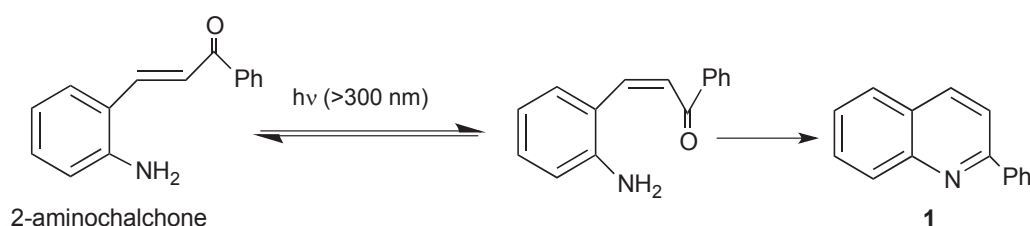
## 2. QUINOLINES

Syntheses of quinolines **1** were generally started from ortho substituted anilines and ketones under acidic or basic conditions at relatively higher temperature. For the synthesis of quinolines, various methods have been reported including the Skraup,<sup>6</sup> Conrad-Limpach-Knorr,<sup>7</sup> Pfitzinger,<sup>8</sup> Friedländer,<sup>9</sup> and Combes reaction.<sup>10</sup> Especially, Friedländer condensation is still considered as a popular method for the synthesis of quinoline derivatives.<sup>11-15</sup> In these methods, 2-aminobenzophenones or 2-aminobenzaldehydes condense with ketones or  $\beta$ -diketones to yield quinolines under acidic or basic conditions (Scheme 1).<sup>16</sup>



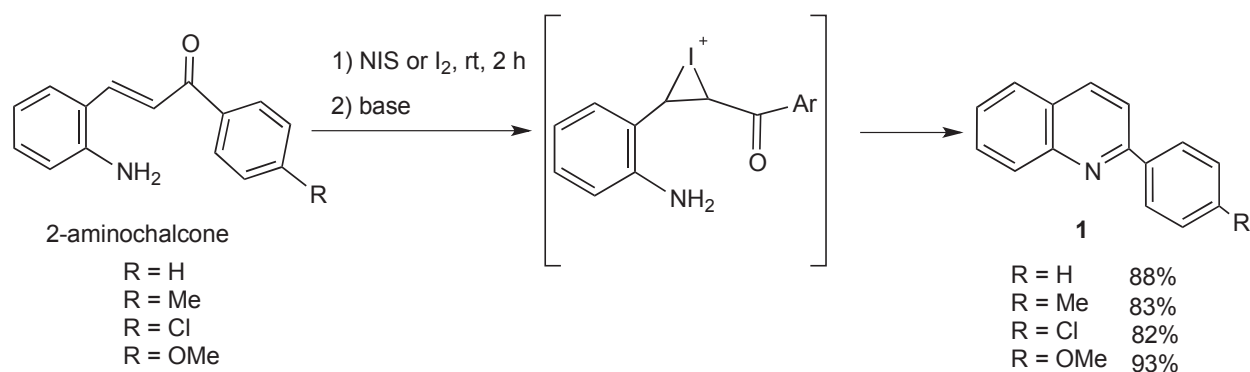
**Scheme 1.** Friedländer quinoline synthesis

However, intramolecular cyclizations of 2-aminochalcones to afford quinolines were relatively rare. The utility of vinylogous aza-Morita-Baylis-Hillman reaction was applied the total synthesis of natural product onychine by Clary and Back.<sup>17</sup> One of the simplest synthesis of quinolines from anilines would be intramolecular photocyclization of 2-alkenylanilines, one of which was reported by Horaguchi *et al.* (Scheme 2). They isomerized *trans*-2-amiochalcone to *cis*-form by photoirradiation, which automatically condensed to give imines (quinolines).<sup>18</sup>



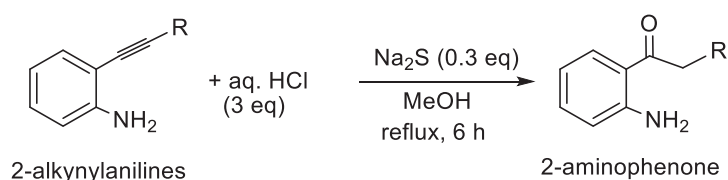
**Scheme 2.** Synthesis of 2-arylquinolines **1** via photocyclization (ref. 18)

We thought that iodine easily add to double bond to afford iodonium intermediates, which cyclized to give the corresponding imines. As expected, the corresponding 2-arylquinolines were obtained in good yields (Scheme 3).<sup>19</sup>



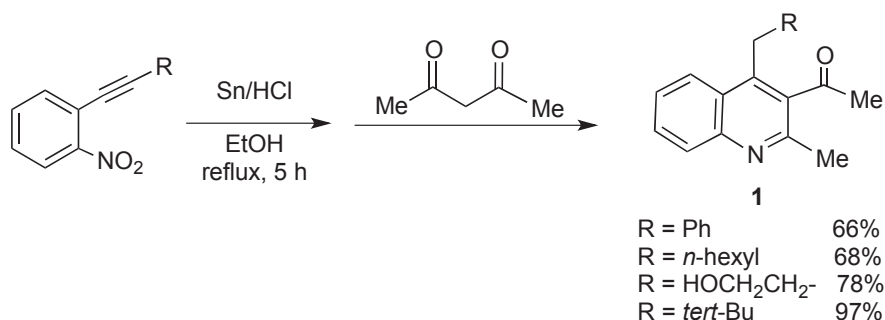
**Scheme 3.** Active halogen mediated cyclization of 2-aminochalcones

We then paid attention to the Friedländer reaction, which produced substituted quinolines from 2-aminobenzaldehyde with methyl ketones under basic conditions. Since substituted 2-alkynylanilines were easily synthesized by Sonogashira coupling reaction, acidic hydrolysis of these anilines easily transferred to 2-aminophenones, which would be useful substrates for substituted quinolines by Friedländer reaction (Scheme 4).<sup>20</sup>



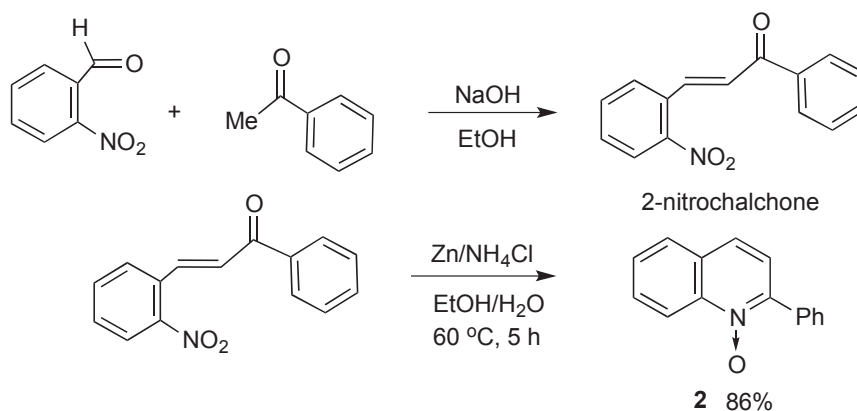
**Scheme 4.** Synthesis of 2-aminophenones from 2-alkynylanilines

By using these 2-aminophenones, the corresponding quinolines were easily synthesized by treating with ketones. Additionally, one-pot synthesis of quinolones was successfully accomplished by using 2-alkynylnitrobenzenes as substrates (Scheme 5).<sup>21</sup> This method would provide a new route toward nitrogen containing multi condensed heterocycles.



**Scheme 5.** One-pot synthesis of substituted quinolones from 2-alkynylnitrobenzenes

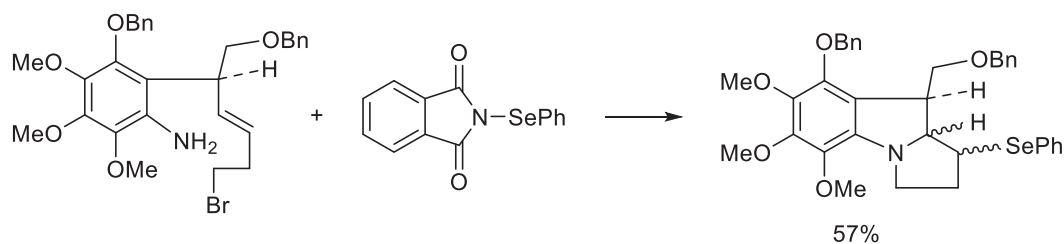
We then tried the synthesis of quinoline *N*-oxides **2**, which were generally prepared by oxidation of quinolines.<sup>22</sup> Although direct Baylis-Hillman adducts reacted with trifluoroacetic acid to give 3,4-substituted quinoline *N*-oxides **2**, there are few reports on the direct synthesis of quinoline *N*-oxides **2** from chalcones or 3-hydroxy ketones.<sup>23</sup> Thus, we have applied the above quinoline synthesis. Since Claisen condensation by reacting 2-nitrobenzaldehyde and acetophenone gave 2-nitrochalcone, we could isolate quinoline *N*-oxides **2** by tuning the metal mediated reduction process in high yields (Scheme 6).<sup>24</sup>



**Scheme 6.** Synthesis of quinoline *N*-oxide **2**

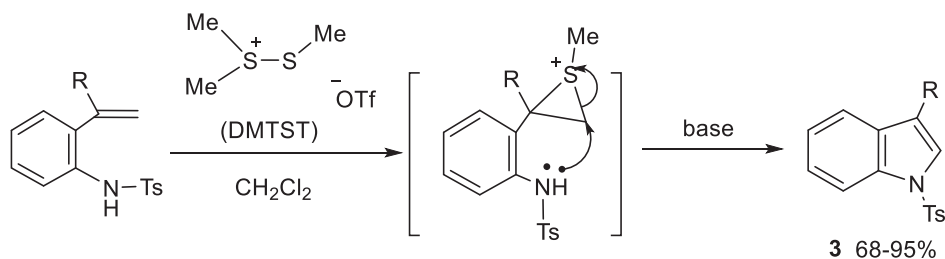
### 3. INDOLES

Intramolecular cyclization of active chalcogen compounds to afford nitrogen containing heterocycles was developed by Trost and Danishefsky (Scheme 7).<sup>25-27</sup>



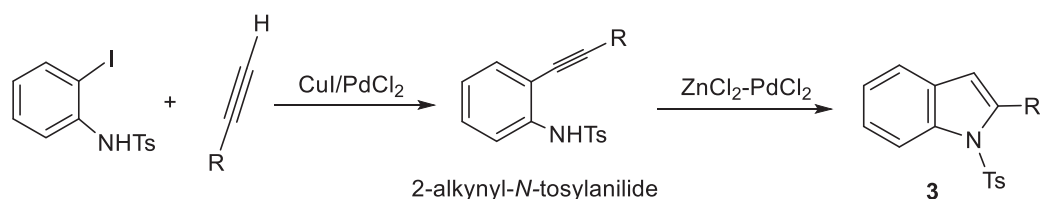
**Scheme 7.** Intramolecular cyclization by Danishefsky (ref. 27)

We have also synthesized *N*-tosylindoles **3** by the intramolecular reaction of dimethylthiomethylsulfonium triflate (DMTST) with *N*-tosylaminostyrene derivatives.<sup>28</sup> *N*-Iodosuccinimide also found to be worked as cyclization mediator (Scheme 8).



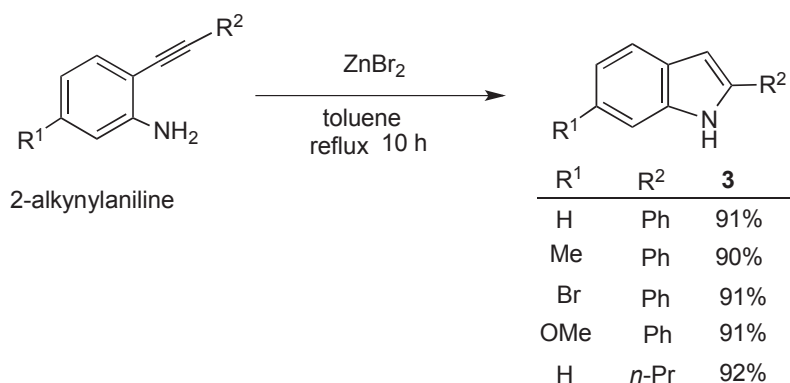
**Scheme 8.** DMTST mediated synthesis of *N*-tosylindoles **3**

2-Alkynylanilines were easily synthesized by Sonogashira coupling reaction of 2-bromoanilines with terminal acetylenes, which would be good precursors of substituted indoles. Many authors synthesized indole derivatives by using palladium catalyzed intramolecular cyclization (Scheme 9).<sup>29</sup>



**Scheme 9.** Palladium catalyzed cyclization of 2-alkynyl-*N*-tosylanilides **3** (ref. 29)

However, not only the palladium-mediated cyclization, but also other reagents ( $\text{ZnCl}_2\text{-PdCl}_2$ , Zn-Cu etc.) are known to have some disadvantages depending on the nature of the reagents, namely, metal alkoxide mediated reactions cannot be applied to the alkaline-sensitive substrates and the carbonyl or sulfonyl groups have to be on the nitrogen atom for most procedures. Thus, we have interested in this cyclization without transition metal catalyst. By using catalytic amount of zinc bromide, 2-substituted indoles were synthesized by the reaction of 2-alkynylanilines with catalytic amount of  $\text{ZnBr}_2$  in high yields (Scheme 10).<sup>30</sup>

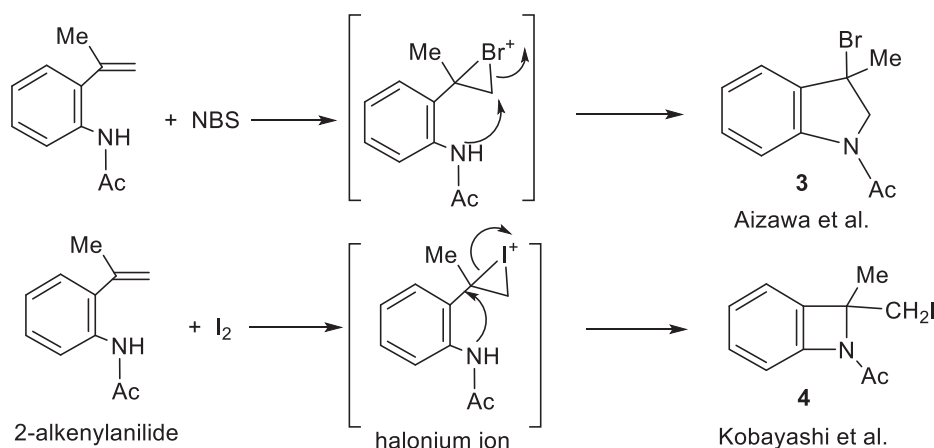


**Scheme 10.**  $\text{ZnBr}_2$  mediated cyclization of 2-alkynylanilines

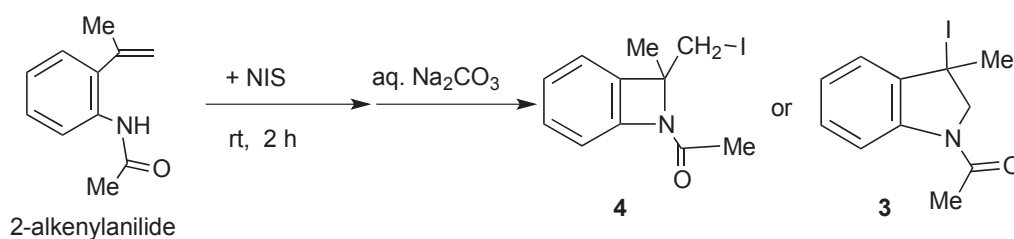
#### 4. BENZOXAZINES

Generally, intramolecular cyclization of substituted aniline derivatives with iodine or *N*-bromosuccinimide (NBS) gave the corresponding nitrogen containing heterocycles such as indoles, benzazetines, and quinolines. Aizawa *et al.* and Kobayashi *et al.* have reported the synthesis of *N*-acylindoles **3** and *N*-acylbenzazetines **4** from the same substrates (Scheme 11).<sup>31,32</sup>

We have interested in the difference in the reactivity between these two reactions, thus the reaction of 2-alkenylanilide with *N*-iodosuccinimide (NIS) in the presence of sodium carbonate was investigated (Scheme 12).

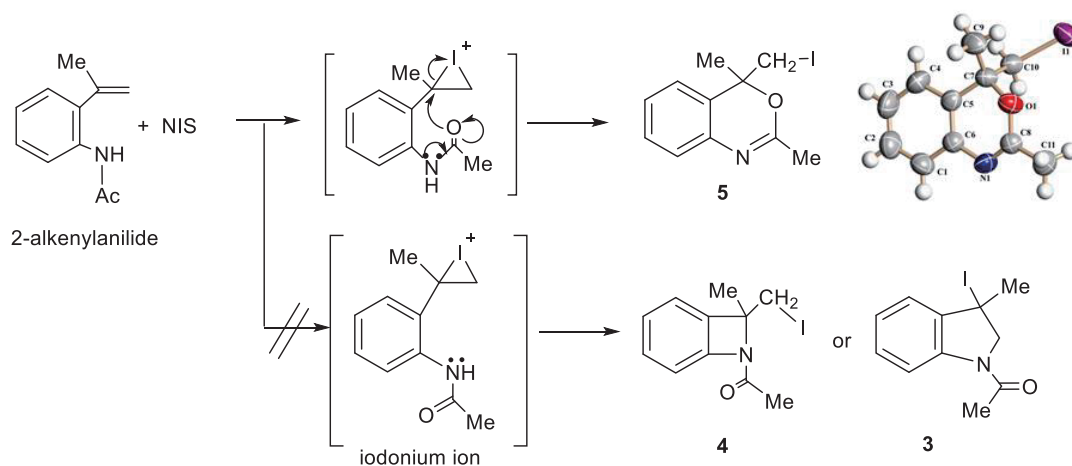


**Scheme 11.** NBS or I<sub>2</sub> mediated cyclization of 2-alkenylanilides (ref. 31, 32)



**Scheme 12.** NIS mediated cyclization of 2-alkenylanilide

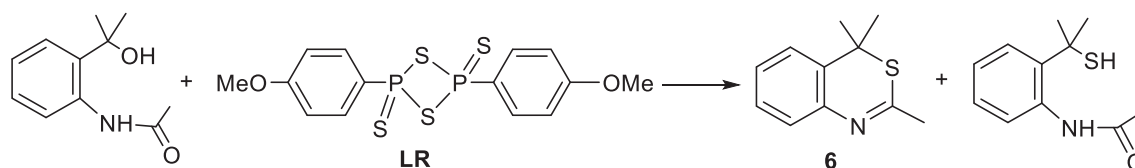
First, we thought that the reaction favored 4-*exo-tet* manner to give benzazetines **4**.<sup>33</sup> However, spectral data shows some ambiguity toward its carbon NMR data. Generally, amide carbon resonate at 173 ppm, whereas this compound shows at 159 ppm. Thus, the structure would not be correct. Finally, we have performed X-ray crystallographic analysis of this compound, which shows new type of cyclized product, benzoxazines **5** (Scheme 13).<sup>19,34</sup> Thus, the reaction proceeded as follows: initially formed iodonium ion was attacked by amide oxygen to give the corresponding iminium ion which finally produced benzoxazine **5**. Other reactions were reacted in a similar manner.



**Scheme 13.** Synthesis of benzoxazines by the reaction of 2-alkenylanilide with NIS

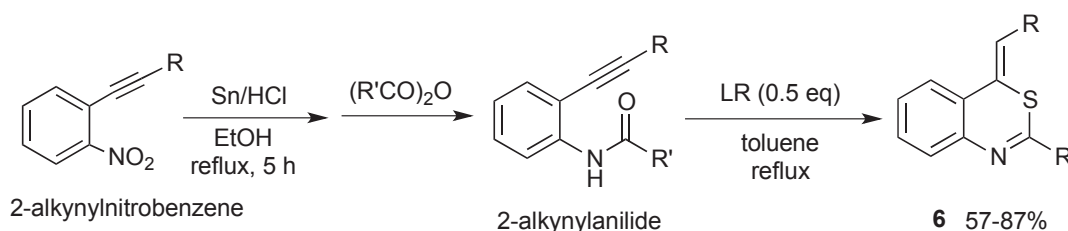
## 5. BENZOTHAZINES

2,4-Bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide, commonly known as Lawesson's reagent (LR), is one of the most famous thionation reagents. LR has also been utilized in the synthesis of five- and six-membered phosphorus heterocycles. By applying this method, Nishio reported the sulfur and nitrogen containing heterocycles such as thiazolines or benzothiazines **6** from *N*-acylaminoalcohols (Scheme 14).<sup>35</sup>



**Scheme 14.** Synthesis of benzothiazines from 2-acylaminoalcohol with LR

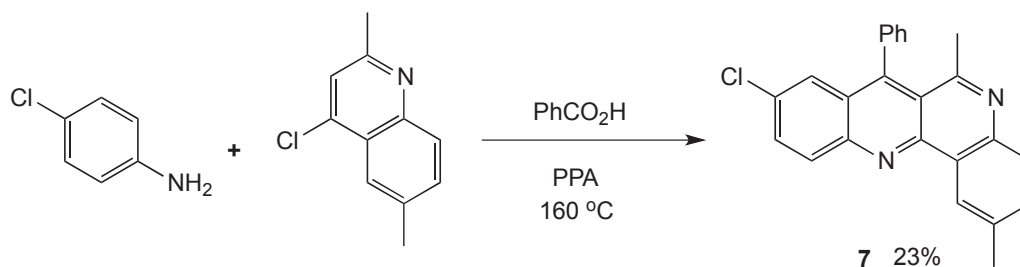
We have interested in the simple synthesis of benzothiazines **6** from 2-alkynylaniline derivatives. By applying this method, we could isolate 3,1-benzothiazines from 2-alkynylanilides with LR (Scheme 15).<sup>36</sup>



**Scheme 15.** Intramolecular cyclization of 2-alkynylanilides with LR

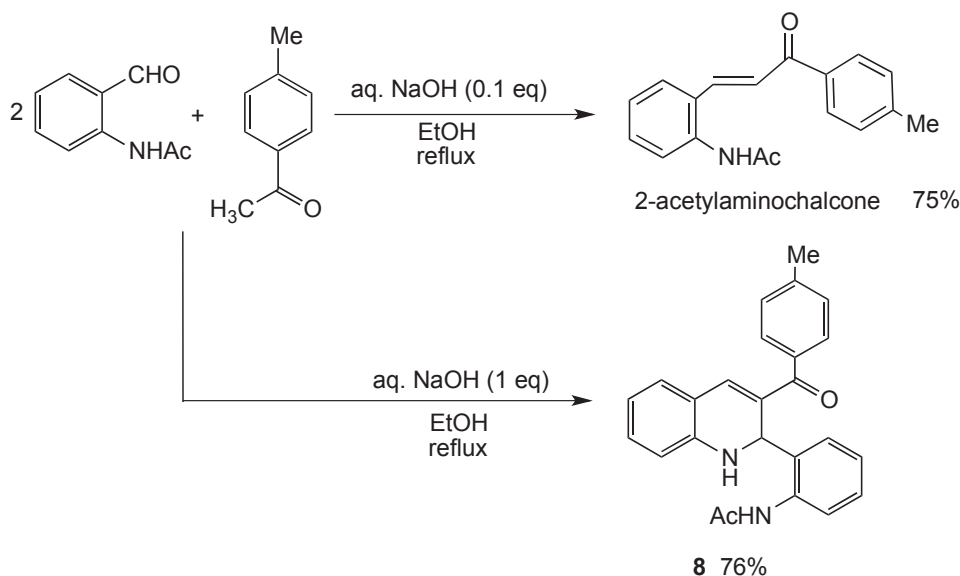
## 6. DIBENZONAPHTHYRIDINES

Methods for the synthesis of dibenzo[*b,h*][1,6]naphthyridines **7** include the reaction of quinolines with 2-aminobenzoic acid or 2-aminoacetophenone<sup>37-38</sup> and the reaction of quinolinones with 2-aminoacetophenones,<sup>39</sup> all of which are based on the Friedländer reaction that proceeds at a high reaction temperature (160-180 °C) with lower yields. Recently, three-component reactions that yielded naphthyridine derivatives were reported.<sup>40-41</sup> It is well known that chalcones are synthesized by the reaction of benzaldehydes with acetophenones in the presence of base.<sup>42</sup> These results prompted us to provide a possibility of one-pot synthesis of dibenzonaphthyridines **7** from 2-acetylaminobenzaldehyde and acetophenones. Previously, these compounds were synthesized from quinolines, aniline, and benzoic acid by high temperature conjugation with low yield (Scheme 16).<sup>43</sup>



**Scheme 16.** Reported synthesis of dibenzonaphthyridines **7** (ref. 47)

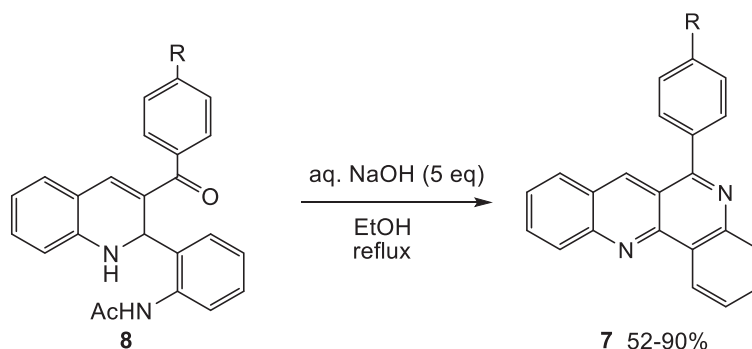
Thus, we intended a practical synthesis of dibenzonaphthyridines **7** from 2-aminobenzaldehydes. Since 2-aminobenzaldehyde is automatically condensed to give polymeric product, 2-acetylaminobenzaldehyde was used as a substrate. When 0.1 eq of aq. NaOH was used in the reaction of 2-acetylaminobenzaldehyde with acetophenone, the corresponding chalcone was obtained. However, when 1 eq. of aq. NaOH was used, 1,2-dihydroquinoline **8** was obtained in 76% yield, which clearly shows that chalcone intermediate further cyclized via intramolecular manner to give 1,2-dihydroquinoline **8** (Scheme 17).



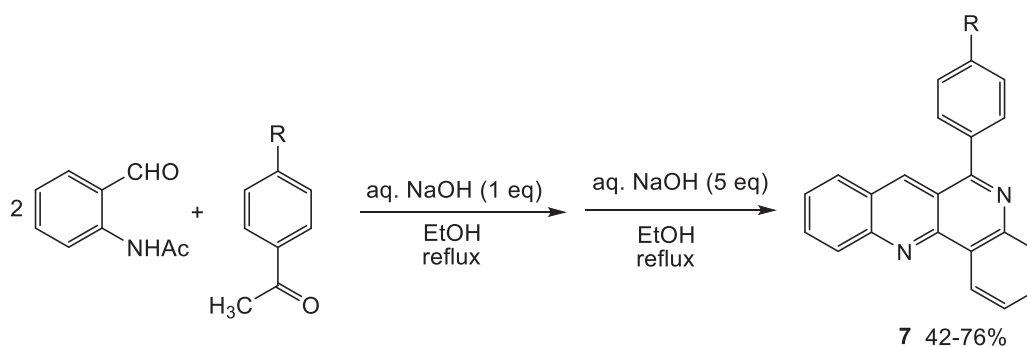
**Scheme 17.** Synthesis of 1,2-dihydroquinoline

Further addition of aq. NaOH finished the formation of dibenzonaphthyridines **7** by intramolecular condensation (Scheme 18a). Finally, one-pot synthesis of dibenzonaphthyridines **7** from 2-acetylaminobenzaldehyde with acetophenones was accomplished by sequential addition of aq. NaOH. Yields were in the range of 42-76% (Scheme 18b). The obtained dibenzonaphthyridine **7** was methylated to give the corresponding ammonium triflate **9**. Dibenzonaphthyridines **7** were selectively methylated at 6-position and their structures were very similar to that of ethidium bromide (EtBr), a

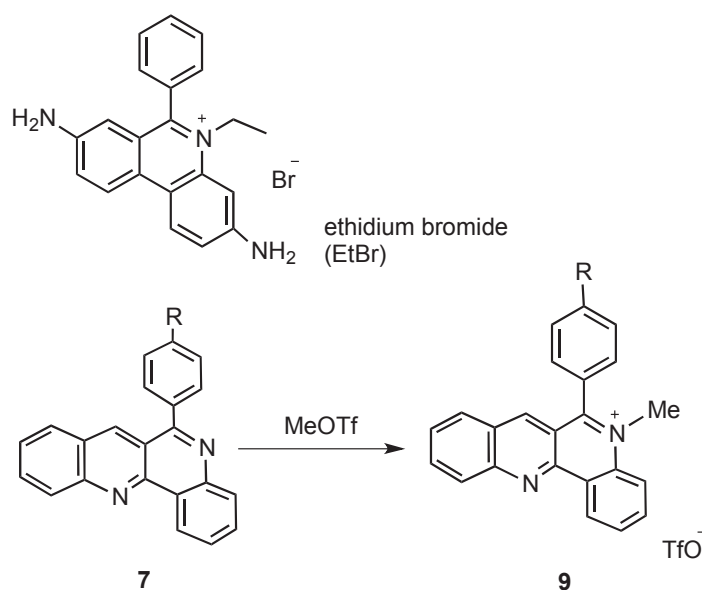
well-known DNA intercalating agent. Thus, we have examined the behavior of spectroscopic and intercalation properties to compare that of EtBr (Scheme 19).<sup>44</sup>



**Scheme 18a.** Synthesis of dibenzonaphthyridines

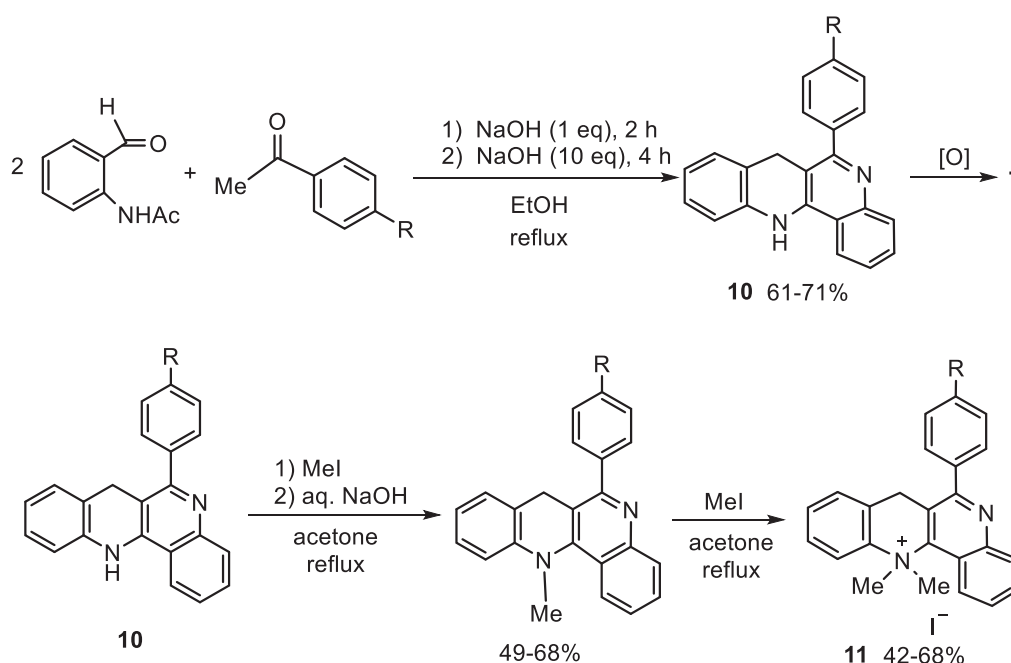


**Scheme 18b.** One-pot synthesis of dibenzonaphthyridines



**Scheme 19.** Methylation of dibenzonaphthyridines

6-Methylated dibenzonaphthyridine **9** exhibited strong fluorescence at 420 nm when irradiated at 360 nm and a titration experiment showed a gradual decrease in the fluorescence intensity in response to the increasing concentration of DNA, which indicated the ability of nitrogen containing planer ring to coordinate to DNA. However, these compounds have disadvantages compared to EtBr. These compounds produce emissions around 420-440 nm in solution, but when they intercalate into DNA, their emission intensity decreased (turn-off), rendering DNA detection difficult. Fortunately, treatment of 2-acetylaminobenzaldehyde with acetophenones in aq. NaOH solution followed by further addition of aq. NaOH resulted in the formation of 1,6-dihydrodibenzonaphthyridines **10**, which are readily oxidized in the air to give dibenzonaphthyridines **7**. Isolated 1,6-dihydrodibenzonaphthyridines **10** were easily methylated by methyl iodide to give 1,1-dimethylammonium salts **11** (Scheme 20).



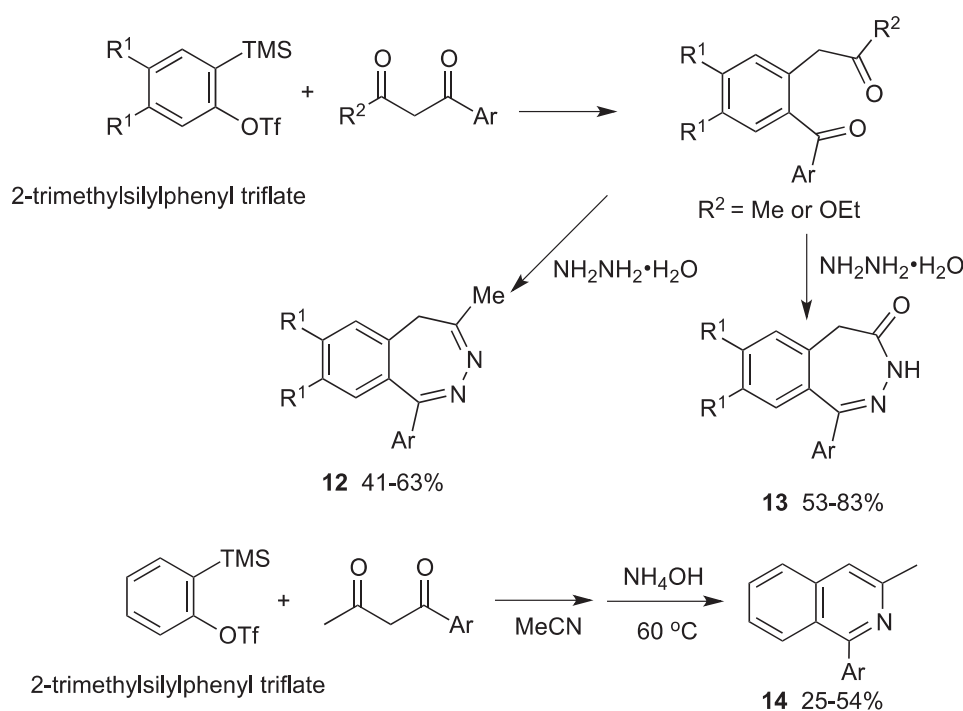
**Scheme 20.** Synthesis of 1,1-dimethyl-1,6-dihydrodibenzonaphthyridium iodide

Inspection of DNA property of these compounds **11** exhibited turn-on property of DNA intercalation.<sup>45</sup>

## 7. BENZODIAZEPINES AND ISOQUINOLINES

Benzodiazepines are one of the important fused bicyclic compounds which have gained attention for their remarkable depressant activity in central nervous system and their being one on the most widely prescribed class of psychotropics.<sup>46,47</sup> 2,3-Benzodiazepines **12** act as tranquilizing agents without any muscle relaxant and anti convulsant activity.<sup>48,49</sup> Previous synthetic methods of these compounds include four-step reactions starting from aryacetones and aryethanols.<sup>50</sup> Recently, we have reported

synthesis of 4-aryl-2-naphthols by reacting 2-(trimethylsilyl)phenyl triflate with  $\beta$ -diketones in the presence of CsF.<sup>51-53</sup> We have applied this method to the synthesis of 2,3-benzodiazepines **12**. Treatment of trimethylsilylphenyl triflate with arylacetones in the presence of CsF resulted in the formation of 2-aryloxyacetophenones, which further reacted with hydrazine hydrate to give 2,3-benzodiazepines **12** in moderate yields. By using ethyl acetoacetate instead of benzoylacetone, 2,3-benzodiazepin-4-ones **13** were synthesized. When trimethylsilylphenyl triflate was treated with benzoylacetones in the presence of fluoride followed by the addition of ammonium hydroxide, the corresponding isoquinolines **14** were obtained in one-pot reaction (Scheme 21).<sup>54</sup>



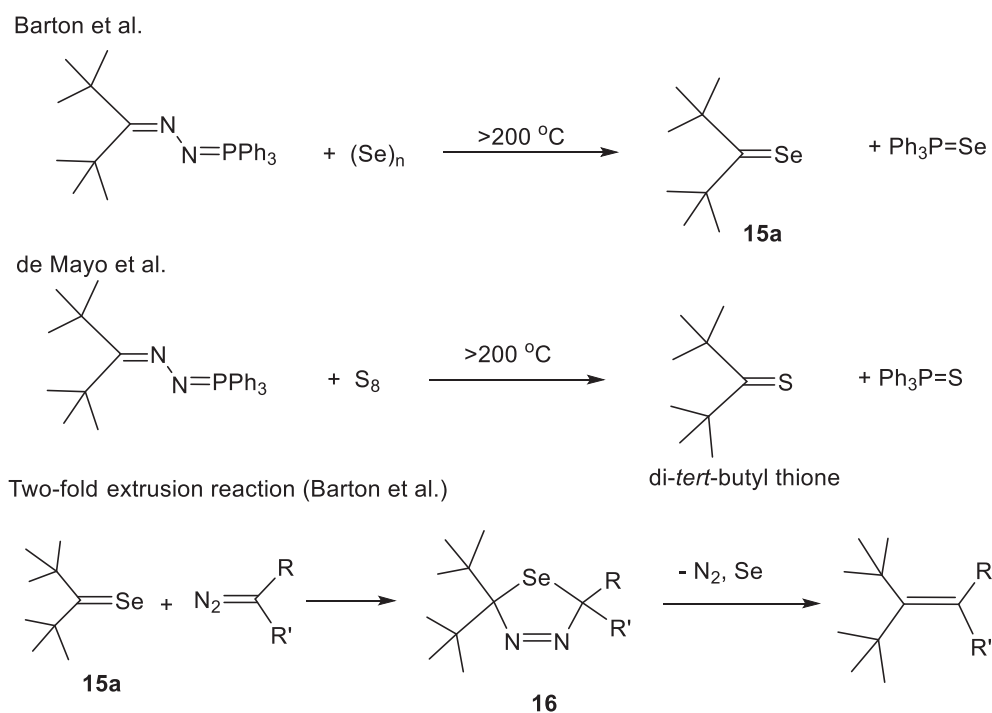
**Scheme 21.** Synthesis of benzodiazepines, benzodiazepin-4-ones, and isoquinolines

Thus, we have synthesized many nitrogen containing heterocycles from imine and its derivatives: quinolines and quinoline *N*-oxides by intramolecular cyclization of 2-aminochalcone derivatives, benzoxazines and benzothiazines from 2-acylaminoalkenyl or alkynylbenzenes, dibenzonaphthyridines from 2-acetylaminobenzaldehyde and acetophenones. Zinc catalyzed intramolecular cyclization of 2-alkenylanilines to indoles was developed. Short-step syntheses of benzodiazepines, benzodiazepine-4-ones, and isoquinolines from benzyne precursors were also accomplished.

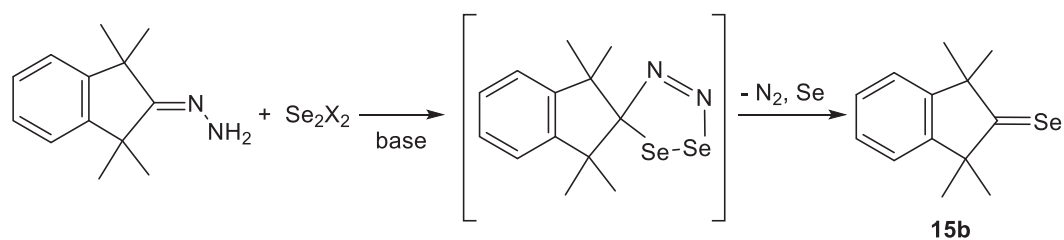
## 8. REACTION OF KETONE HYDRAZONES WITH CHALCOGEN DERIVATIVES

Cyclic selenides and tellurides have received considerable attention due to their application in material

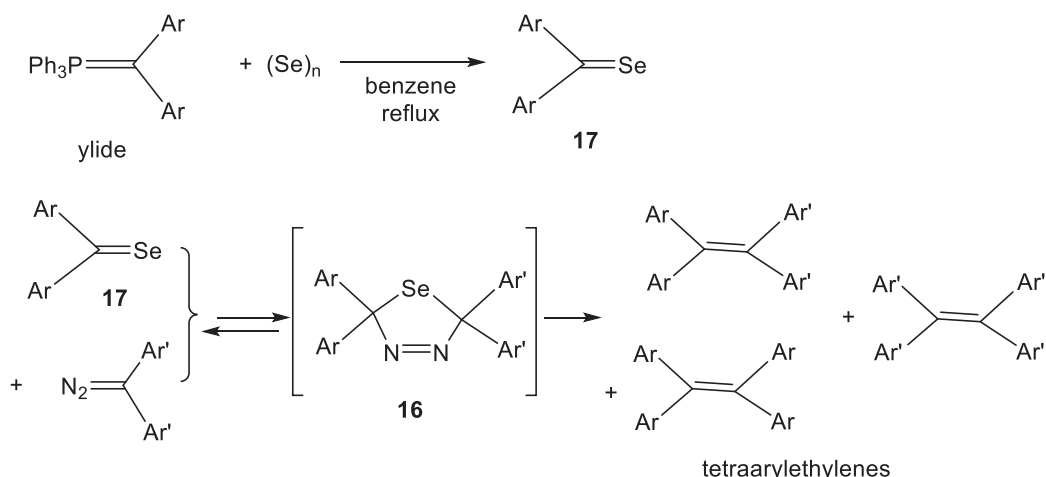
chemistry.<sup>55-57</sup> In 1975, synthesis of sterically crowded alkenes by two-fold extrusion process was reported by Barton and coworkers.<sup>58</sup> They developed new synthesis of sterically crowded selones **15** by the reaction of ketone triphenylphosphoranylidenehydrazones with elemental selenium at high temperature, which reacted with diazoalkanes to give the corresponding 1,3,4-selenadiazolines **16**. Thermolysis of 1,3,4-selenadiazolines **16** gave sterically crowded alkenes via two-fold extrusion process.<sup>59</sup> Although the yields were relatively low, this is the first practical synthesis of selones. Sterically crowded thiones were also synthesized by a similar method (Scheme 22). More practical synthetic method for selones **15** was developed by Okazaki *et al.* and Guziec *et al.*<sup>61,62</sup> They isolated sterically crowded selones **15** by the reaction of ketone hydrazones with diselenium dihalides, yields of which were 50-90% (Scheme 23). We have independently developed the synthesis of diaryl selones **17** by the reaction of diarylmethylenetriphenylphosphorane (ylide) with elemental selenium,<sup>63,64</sup> which reacted with diazoalkanes to give tetraarylethylenes at room temperature (Scheme 24).<sup>65,66</sup>



**Scheme 22.** Two-fold extrusion reaction by using selones (ref. 59, 60)



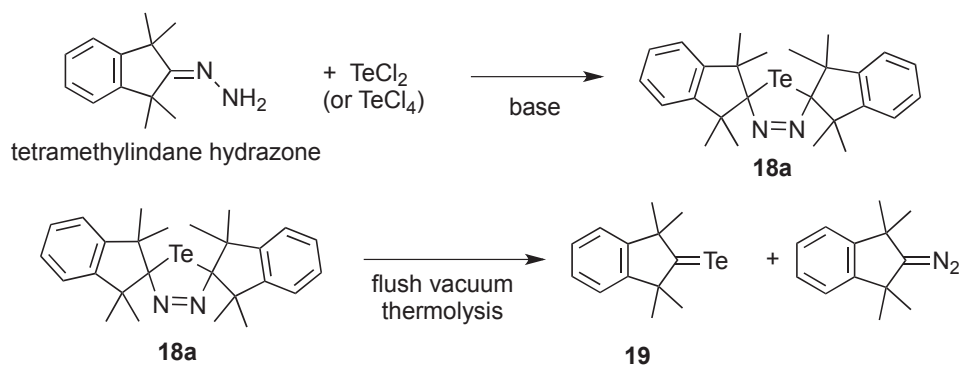
**Scheme 23.** Synthesis of sterically crowded selone (ref. 61, 62)



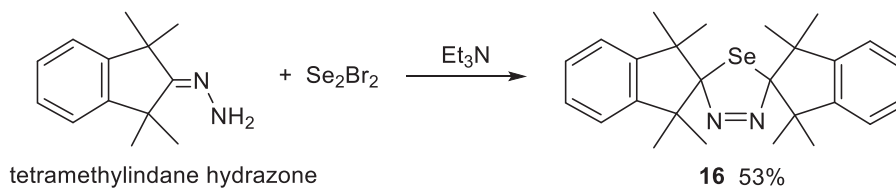
## 9. 1,3,4-SELENADIAZOLINES

1,3,4-Thiadiazolines and 1,3,4-selenadiazolines **16** were generally synthesized by the reaction of diazoalkanes with thiones or selones.<sup>60,67</sup> Interestingly, Okazaki *et al.* developed one-pot synthesis of 1,3,4-telluradiazoline **18a** by the reaction of sterically hindered tetramethylindane hydrazone with  $\text{TeCl}_2$  or  $\text{TeCl}_4$ , presumably, both diazoalkane and telone were formed as intermediates, which coupled via 1,3-dipolar cycloaddition manner to give 1,3,4-telluradiazoline.<sup>68</sup> Thermolysis of the obtained 1,3,4-telluradiazoline **18a** gave relatively unstable tetramethylindane tellone **19** (Scheme 25).<sup>69</sup>

1,3,4-Telluradiazoline and Telone (Okazaki *et al.*)



We have also found that 1,3,4-selenadiazoline **16** were isolated by the reaction of tetramethylindane hydrazone with  $\text{Se}_2\text{Br}_2$  in the presence of triethylamine (Scheme 26). This result indicated that selone **15** and simultaneously formed diazoalkane coupled to afford 1,3,4-selenadiazoline **16** in one-pot operation.<sup>70</sup>

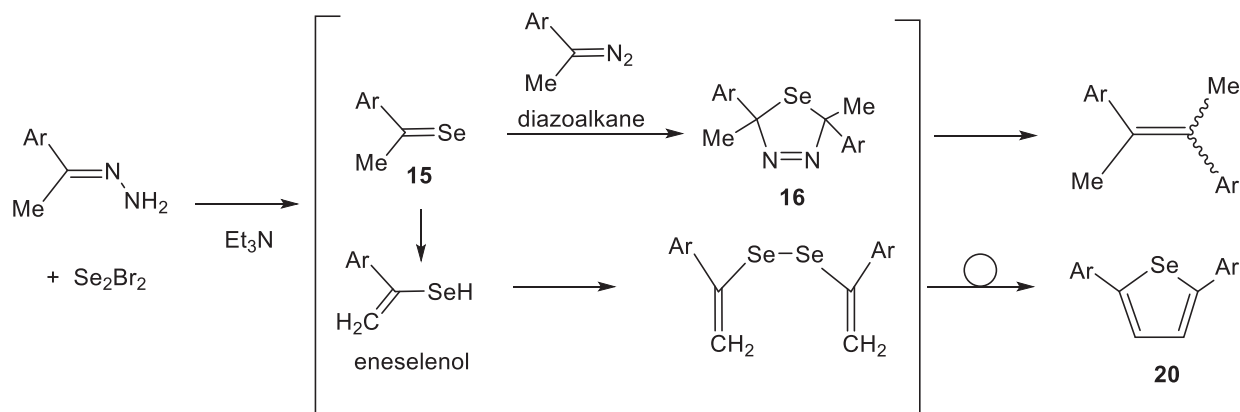


**Scheme 26.** One-pot synthesis of 1,3,4-selenadiazolines

Thermolysis of 1,3,4-selenadiazolines **16** gave the corresponding sterically conjugated alkenes by two-fold extrusion.

### 10. 2,5-DIARYLSELENOPHENE

2,5-Diarylselenophenes **20** are generally synthesized by the reaction of 1,3-diynes with hydrogen selenide,<sup>71</sup> the reaction of arylacetylenes with 1,2,3-selenadiazoles,<sup>72</sup> or the reaction of titanocycles with selenium diselenocyanate.<sup>73</sup> We intended more simple synthesis of 2,5-diarylselenophenes by thermolysis of vinylselenols (eneselenols), which would be easily obtained in situ by the reaction of acetophenone hydrazones with Se<sub>2</sub>Br<sub>2</sub>. When acetophenone hydrazones were treated with Se<sub>2</sub>Br<sub>2</sub> in the presence of triethylamine in refluxing benzene, 2,5-diarylselenophenes **20** were obtained moderately along with alkenes, which clearly shows that both diazoalkanes and selones **15** were formed as intermediates (Scheme 27).<sup>74</sup>

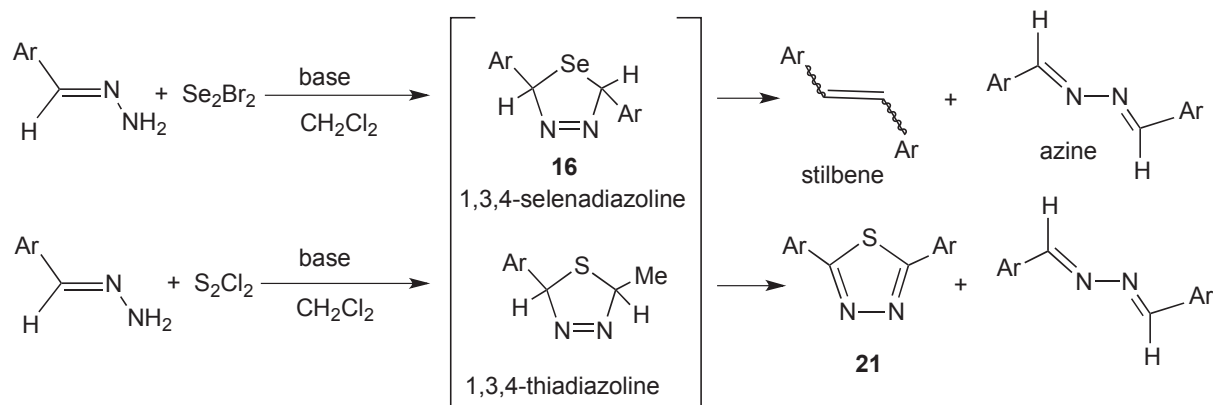


**Scheme 27.** Synthesis of 2,5-diarylselenophenes

### 11. 1,3,4-THIADIAZOLES

The unique reactivity of ketone hydrazones prompted us to investigate the reactivity of aldehyde hydrazones with chalcogen halides. Although the reaction of benzaldehyde hydrazone with Se<sub>2</sub>Br<sub>2</sub> gave a mixture of *trans*- and *cis*-stilbene, the reaction with S<sub>2</sub>Cl<sub>2</sub> gave the corresponding

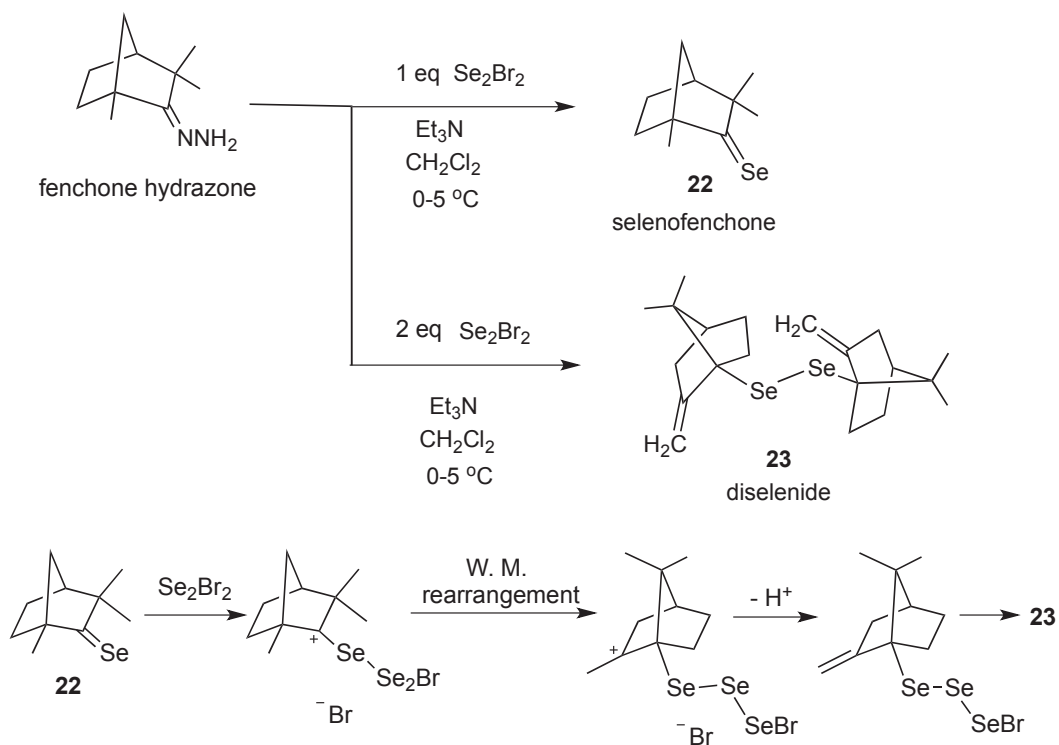
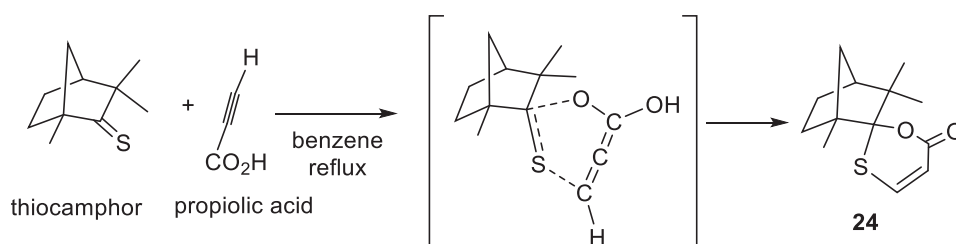
2,5-diphenyl-1,3,4-thiadiazole **21** in 54% yield along with azines (Scheme 28). These results showed that 1,3,4-selenidiazoline and 1,3,4-thiadiazoline were formed as intermediates.<sup>75</sup>



Scheme 28. Synthesis of 2,5-diaryl-1,3,4-thiadiazoles

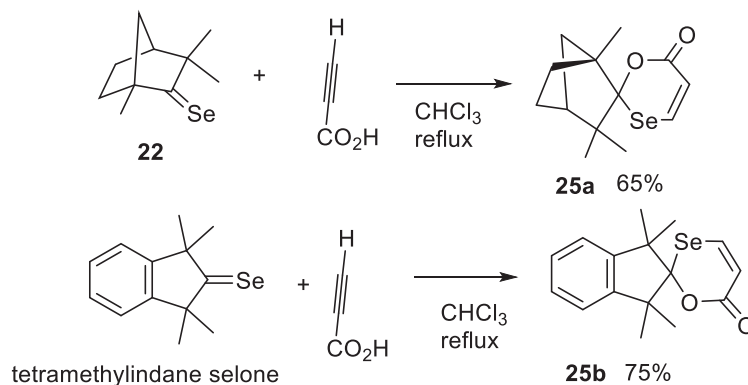
## 12. WAGNER-MEERWEIN REARRANGEMENT

Okazaki and Guzic reported the synthesis of selenofenchesones **22** by reacting fenchone hydrazones with diselenium dihalides in the presence of bases.<sup>61,62</sup> Thiofenchone was also synthesized by using fenchone hydrazone with  $\text{S}_2\text{Cl}_2$ . Although this is a useful method for the synthesis of sterically crowded selones **15** and thiones, we have found an interesting result. When equal amount of  $\text{Se}_2\text{Br}_2$  was reacted with fenchone hydrazone, selenofenchone **22** was obtained in 50% yield, whereas diselenide (Wagner-Meerwein rearranged product **23**) was isolated by using 2 eq of  $\text{Se}_2\text{Br}_2$ , which suggested that excess  $\text{Se}_2\text{Br}_2$  plays as a Lewis acid. Selenofenchone intermediate **22** reacted with  $\text{Se}_2\text{Br}_2$  to give cationic intermediate, which rearranged via Wagner-Meerwein (W. M.) manner to give diselenide **23** (Scheme 29).<sup>76</sup> By using sterically crowded thiones, we have developed new type of heterocycles, thiodioxenones **24** by reaction with propionic acid derivatives via concerted mechanism (Scheme 30).<sup>77,78</sup>

Scheme 29. Reaction of fenchone hydrazone with  $\text{Se}_2\text{Br}_2$ 

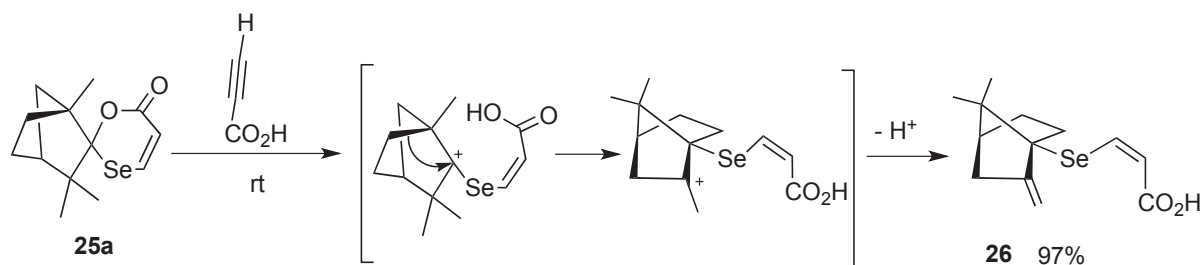
Scheme 30. Synthesis of thiodioxenones

Selenofenchone **22** also reacted with propiolic acid to give selenodioxenone **25a** in 65% yield (Scheme 31).<sup>79</sup>



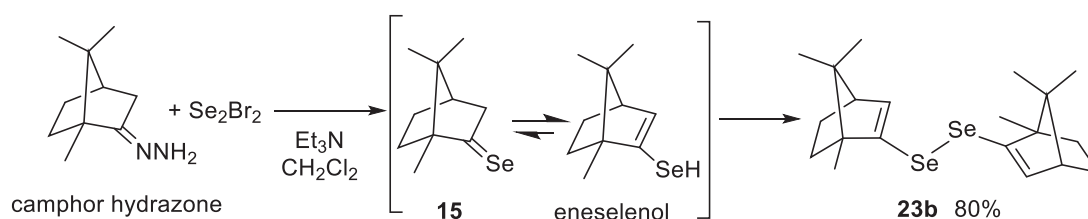
Scheme 31. Synthesis of selenodioxenones

When selenodioxenone **25a** derived from selenofenchone **22** was treated with excess amount of propiolic acid in refluxing toluene, Wagner-Meerwein rearrangement followed by  $\alpha$ -hydrogen abstraction produced bridge-head selenide **26** (Scheme 32).<sup>80</sup>



**Scheme 32.** Wagner-Meerwein rearrangement of selenodioxenone

When camphor hydrazone was treated with  $\text{Se}_2\text{Br}_2$ , initially formed selenocamphor **15** was tautomerized to give eneselenol, which easily oxidized to give diselenide **23b** (Scheme 33).<sup>81</sup>



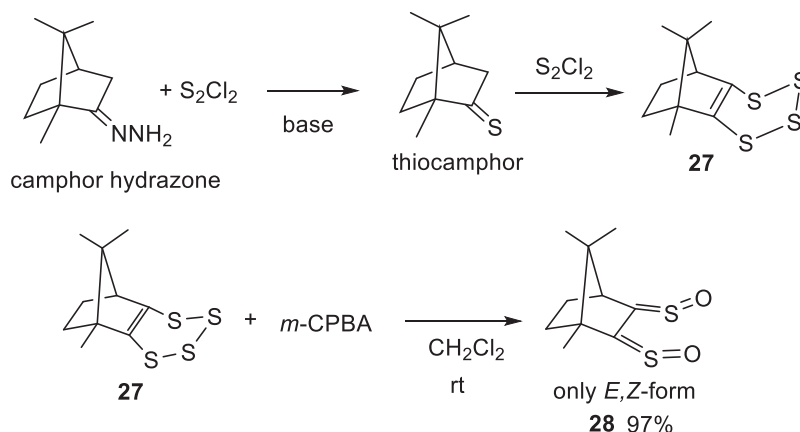
**Scheme 33.** Reaction of camphor hydrazone with  $\text{Se}_2\text{Br}_2$

The same product was obtained by the reaction of camphor tosylhydrazone with elemental selenium at high temperature, however, the yield was low.<sup>82</sup>

### 13. CYCLIC POLYSULFIDES

Tetrathiins **25** are novel six-membered cyclic tetrasulfides that are synthesized by reacting sterically hindered alkynes with elemental sulfur and alkenes with  $\text{S}_2\text{Cl}_2$ .<sup>83</sup> However, there was no report on the synthesis of cyclic polysulfides containing norbornane skeleton. We have already reported the novel cyclic 4-membered 1,2-dithietan-3-one by the reaction of  $\alpha$ -dithiolactone with nitrile oxide via cycloaddition process.<sup>84</sup> In the course of our research on the reactivity of ketone hydrazones with chalcogen halides, we have interested in the reaction of camphor hydrazone with  $\text{S}_2\text{Cl}_2$  because camphor is well known to react with Lewis acids to afford the corresponding Wagner-Meerwein rearranged products.<sup>85</sup> Treatment of camphor hydrazone with  $\text{S}_2\text{Cl}_2$  in the presence of triethylamine resulted in the formation of cyclic polysulfide (1,2,3,4-tetrathiin **27**). The obtained cyclic polysulfide containing

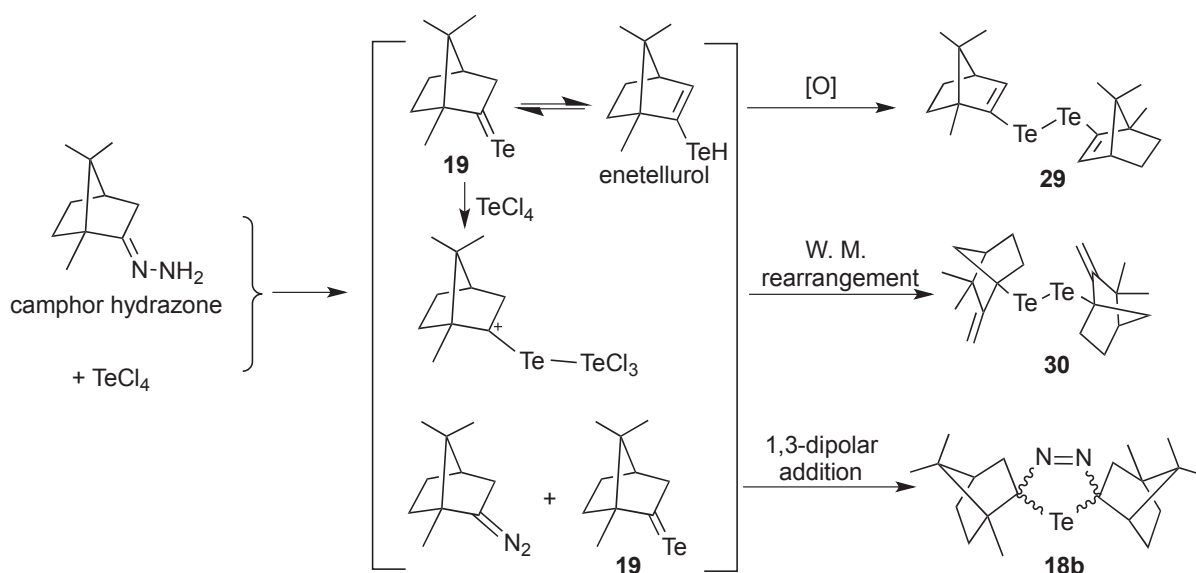
norbornane skeleton is the first example.<sup>86</sup> Interestingly, oxidation by *m*-CPBA of tetrathiin **27** gave the corresponding  $\alpha$ -disulfine **28** with complete stereoselectivity in almost quantitative yield (Scheme 34).<sup>87</sup>



**Scheme 34.** Reaction of camphor hydrazone with  $S_2Cl_2$

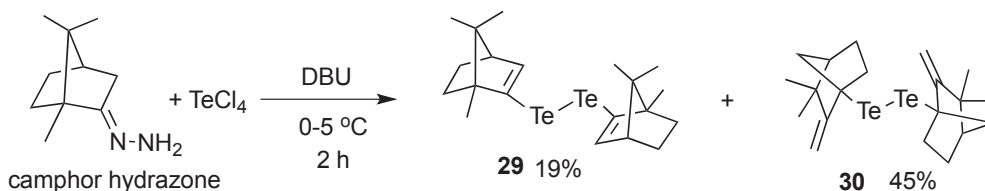
#### 14. REACTION OF CAMPHOR AND FENCHONE HYDRAZONE WITH TELLURIUM TETRACHLORIDE

Our attention was tuned to the reaction of camphor hydrazone with  $TeCl_4$  because three possible reaction pathways would proceed: formation of 1,3,4-telluradiazoline intermediate **18b** via 1,3-dipolar cycloaddition, ditelluride (enetellurol product **29**), or Wagner-Meerwein rearranged product **30** (Scheme 35).



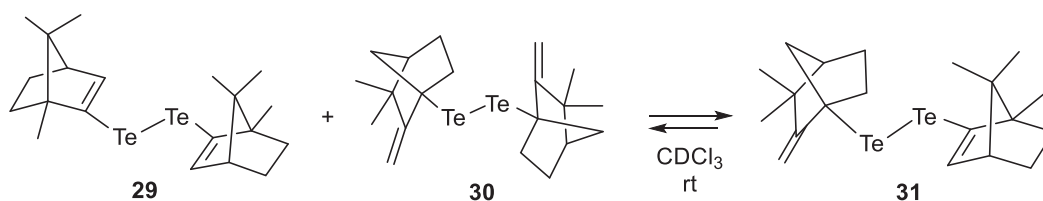
**Scheme 35.** Three possible pathways from the reaction of camphor hydrazone with  $TeCl_4$

Thus, we have tried this reaction in dichloromethane solution at 0 °C. Treatment of camphor hydrazone with  $\text{TeCl}_4$  in the presence of DBU gave two types of ditellurides, enetellurol product **29** and Wagner-Meerwein rearranged product **30** (Scheme 36).



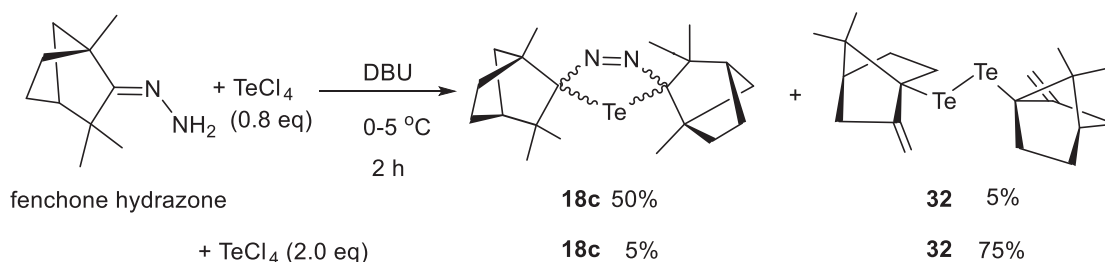
**Scheme 36.** Formation of two ditellurides

This result clearly suggested that both  $\alpha$ -proton abstraction and Wagner-Meerwein rearrangement reaction occurred in the reaction. When isolated these two ditellurides **29** and **30** were mixed in solution, unsymmetrical ditelluride **31** was formed in solution, whereas isolation of unsymmetrical ditellurides **31** was failed (Scheme 37). Only symmetrical ditellurides were isolated, which showed that disproportionation between two ditellurides occurred in solution via radical mechanism.<sup>88</sup>



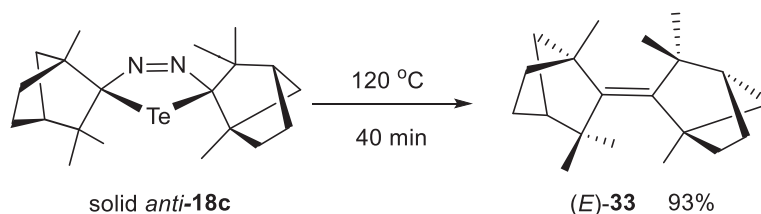
**Scheme 37.** Disproportionation reaction of ditellurides in solution

We then tried the reaction of fenchone hydrazone with  $\text{TeCl}_4$  whether similar ditelluride would be formed. The result was quite different from that of camphor hydrazone. When 0.8 eq of  $\text{TeCl}_4$  was used, the corresponding 1,3,4-telluradiazoline **18c** was obtained as a main product, whereas 2.0 eq of  $\text{TeCl}_4$  resulted in the formation of ditelluride (Wagner-Meerwein rearranged product **32**) in 75% (Scheme 38). The result clearly showed that excess  $\text{TeCl}_4$  plays as a Lewis acid to form Wagner-Meerwein rearranged product.



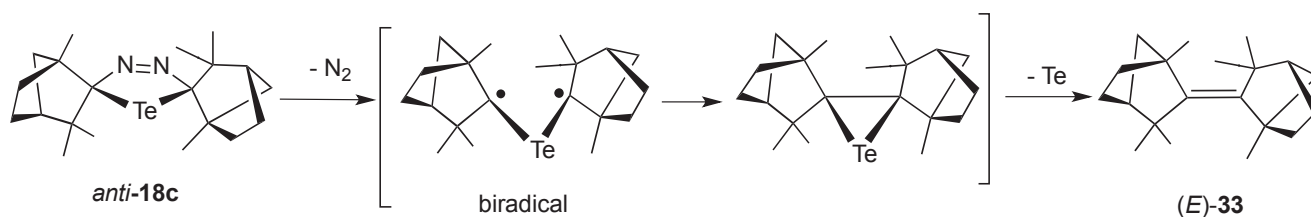
**Scheme 38.** Reaction of fenchone hydrazone with  $\text{TeCl}_4$

Since the obtained 1,3,4-telluradiazoline **18c** were *anti*- and *syn*- mixture, successful isolation of these compounds would provide a mechanistic insight into the two-fold extrusion. We then tried thermolysis of isolable *anti*-isomer **18c** because the mechanism of two-fold extrusion was not precisely examined previously. If the thermolysis of new enantiomerically pure *anti*-1,3,4-telluradiazoline **18c** gave only one product, the reaction would proceed stereoselectively. When solid *anti*-1,3,4-telluradiazoline **18c** was heated at 120 °C under nitrogen atmosphere, (*E*)-1,1',3,3,3',3'-hexamethyl-2,2'-binorbonylidene **33** was formed exclusively (93%), suggesting that the reaction proceeded with perfect stereoselectivity (Scheme 39). (*E*)-**33** was found to have the *E*-form by comparing its spectra with the authentic spectra of the product of the reaction of fenchone triphenylphosphoranylidenehydrazone with elemental selenium.<sup>89</sup> When the reaction was performed in refluxing toluene for 12 h, the same (*E*)-alkene **33** was obtained stereoselectively.



**Scheme 39.** Thermolysis of *anti*-1,3,4-telluradiazoline **18c**

These results clearly indicated that the reaction initially extruded nitrogen molecule to afford the corresponding epitelluride stereospecifically, via a biradical intermediate. Unstable epitelluride immediately released tellurium to give final alkene (*E*)-**33** (Scheme 40).<sup>90</sup>

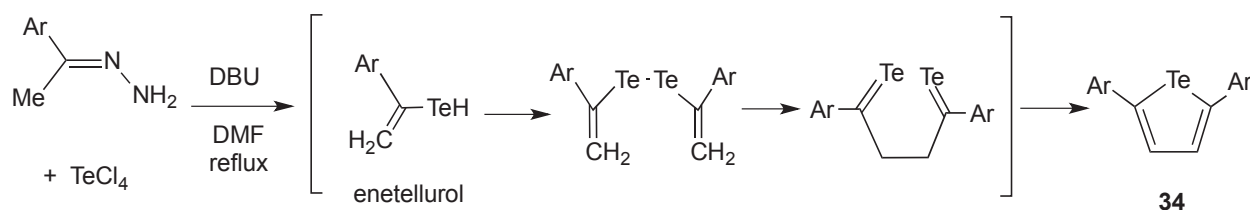


**Scheme 40.** Reaction mechanism

## 15. TELLUROPHENES

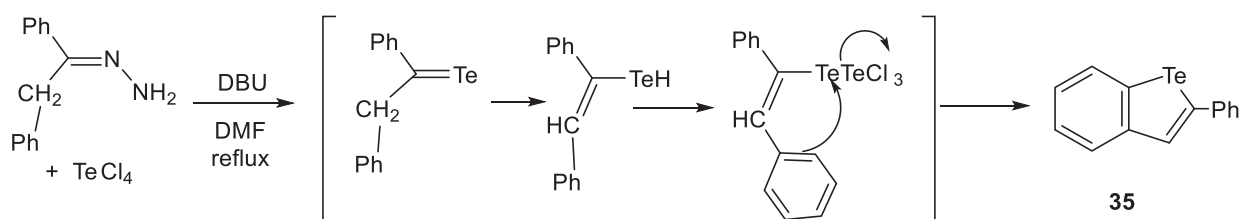
Tellurophenes were previously synthesized by the reaction of dilithio-1,3-butadienes with TeCl<sub>4</sub>,<sup>91</sup> reaction of 1,3-butadiynes with Na<sub>2</sub>Te, reaction of 1,4-bis(butyltelluro)-1,3-butadiene with butyllithium,<sup>92</sup> and reaction of Cp<sub>2</sub>Zr with acetylenes and TeCl<sub>2</sub>.<sup>93</sup> Generally, starting substances required multi-step synthesis. Thus, the synthesis of tellurophene by the use of easily available starting materials would be desirable. As shown in Chapter 10, we have already reported the synthesis of selenophenes by

the reaction of acetophenone hydrazones with  $\text{Se}_2\text{Br}_2$  in the presence of bases, which prompted us to investigate the reaction of acetophenone hydrazones with  $\text{TeCl}_4$ . If telluroacetophenone was formed, it easily converted to enetellurol, thermolysis of which would produce 2,5-diaryltellurophene **34**. After several trials of reaction conditions, 2,5-diaryltellurophenes were obtained by reacting hydrazone with  $\text{TeCl}_4$  in refluxing DMF, whereas propiophenone hydrazone gave only the corresponding ditelluride and monotelluride (Scheme 41).



**Scheme 41.** Reaction of acetophenone hydrazone with  $\text{TeCl}_4$

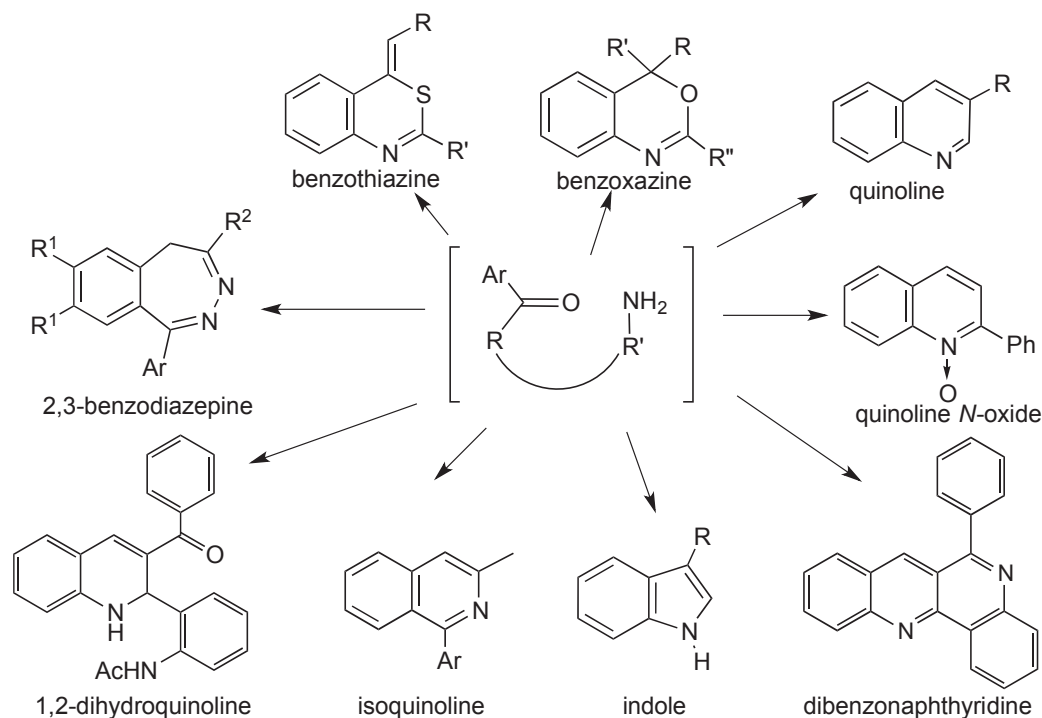
Interestingly, 1,2-diphenylethanone hydrazone reacted with  $\text{TeCl}_4$  to afford 2-phenylbenzotellurophene **35** and *trans*-stilbene in 45% and 25% yields, respectively (Scheme 42).<sup>94</sup>



**Scheme 42.** Synthesis of 2-phenylbenzotellurophene

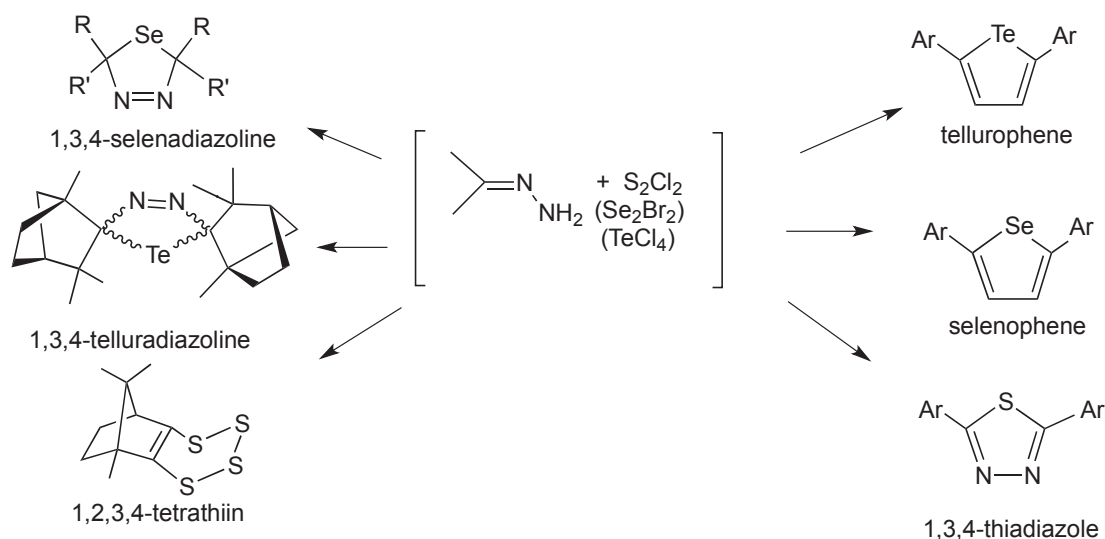
## 16. CONCLUSION

Formation of carbon-nitrogen double bonds by the reaction of amines with carbonyl compounds to give nitrogen containing heterocycles was old-fashioned synthetic method, however, recent progress of multi-component process provided a fascinating synthetic method for nitrogen containing heterocycles. By using this method, we have synthesized quinoline, indoles, benzoxazines, benzothiazines, dibenzonaphthyridines, benzodiazepines, and isoquinolines (Scheme 43).



**Scheme 43.** Nitrogen containing heterocycles via intra- or intermolecular cyclization

Ketone hydrazones are also very interesting compounds due to their versatile reactivity. We have developed the synthesis of chalcogen containing heterocycles such as 1,3,4-thiadiazole, 1,3,4-selenadiazolines, 1,3,4-telluradiazolines, selenophenes, tellurophenes, disulfides, cyclic polysulfides, diselenides, and ditellurides (Scheme 44).



**Scheme 44.** Heterocycles from ketone or aldehyde hydrazones

The new procedures allow us to obtain a variety of N, O, S, Se, and Te containing heterocycles.

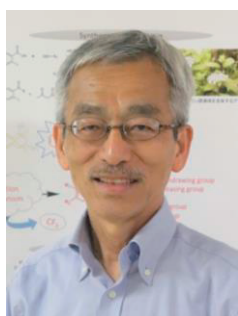
## REFERENCES

1. M. P. Maguire, K. R. Sheets, K. McVety, A. P. Spada, and A. Zilberstein, *J. Med. Chem.*, 1994, **37**, 2129.
2. A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluháčková, and P. Kočovský, *Org. Lett.*, 2007, **9**, 5473.
3. M. A. E. Shaban, M. A. M. Taha, and E. M. Sharshira, *Adv. Heterocycl. Chem.*, 1991, **52**, 1.
4. 'Name Reactions in Heterocyclic Chemistry,' ed. by J.-J. Li and E. J. Corey, Wiley, Hoboken, N. J., 2005.
5. R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874.
6. R. H. F. Manske and M. Kulka, *Org. React.*, 1953, **7**, 80.
7. N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocycl. Chem.*, 1966, **3**, 222.
8. W. Pfitzinger, *J. Prakt. Chem.*, 1886, **33**, 100.
9. E. A. Fehnel, *J. Org. Chem.*, 1966, **31**, 2899.
10. E. Roberts and E. E. Turner, *J. Chem. Soc.*, 1927, 1832.
11. J. S. Yadav, P. P. Rao, D. Sreenu, R. S. Rao, V. N. Kumar, K. Nagaiah, and A. R. Prasad, *Tetrahedron Lett.*, 2005, **46**, 7249.
12. J. Wu, H.-G. Xia, and K. Gao, *Org. Biomol. Chem.*, 2006, **4**, 126.
13. A. Arcadi, M. Chiarini, S. di Giuseppe, and F. Marinelli, *Synlett*, 2003, 203.
14. S. J. Song, S. J. Cho, D. K. Park, T. W. Kwon, and S. A. Jenekhe, *Tetrahedron Lett.*, 2003, **44**, 255.
15. S. S. Palimkar, S. A. Siddiqui, T. Daniel, R. J. Lahoti, and K. V. Srinivasan, *J. Org. Chem.*, 2003, **68**, 9371.
16. P. Friedländer, *Chem. Ber.*, 1882, **15**, 2572.
17. K. N. Clary and T. G. Back, *Synlett*, 2010, 2802.
18. T. Horaguchi, N. Hosokawa, K. Tanemura, and T. Suzuki, *J. Heterocycl. Chem.*, 2002, **39**, 61.
19. K. Okuma, T. Yasuda, K. Shioji, and Y. Yokomori, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 1824.
20. M. L. Chapdelaine, P. J. Warwick, and A. Shaw, *J. Org. Chem.*, 1989, **54**, 1218.
21. K. Okuma, S. Ozaki, J. Seto, N. Nagahora, and K. Shioji, *Heterocycles*, 2010, **81**, 935.
22. N. K. Jana and J. G. Verkade, *Org. Lett.*, 2003, **5**, 3787.
23. K. Y. Lee, J. M. Kim, and J. N. Kim, *Tetrahedron*, 2003, **59**, 385.
24. K. Okuma, J. Seto, N. Nagahora, and K. Shioji, *J. Heterocycl. Chem.*, 2010, **47**, 1372.
25. B. M. Trost and E. Murayama, *J. Am. Chem. Soc.*, 1981, **103**, 6529.
26. S. V. Ley and B. Lygo, *Tetrahedron Lett.*, 1982, **23**, 4625.
27. S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge, and B. E. Segmuller, *J. Am. Chem. Soc.*, 1985, **107**, 3891.

28. K. Okuma, I. Takeshita, T. Yasuda, and K. Shioji, *Chem. Lett.*, 2006, **35**, 1122.
29. M. Nakamura, L. Ilies, S. Otsubo, and E. Nakamura, *Org. Lett.*, 2006, **8**, 2803.
30. K. Okuma, J. Seto, K. Sakaguchi, S. Ozaki, N. Nagahora, and K. Shioji, *Tetrahedron Lett.*, 2009, **50**, 2943.
31. M. Arisawa, Y. Ando, M. Yamanaka, M. Nakagawa, and A. Nishida, *Synlett*, 2002, 1514.
32. K. Kobayashi, K. Miyamoto, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 886.
33. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
34. K. Okuma, T. Yasuda, I. Takeshita, K. Shioji, and Y. Yokomori, *Tetrahedron*, 2007, **63**, 8250.
35. T. Nishio, *J. Org. Chem.*, 1997, **62**, 1106.
36. K. Okuma, S. Ozaki, N. Nagahora, and K. Shioji, *Heterocycles*, 2011, **83**, 1303.
37. A. A. Avestisyan, I. L. Aleksanyan, and L. P. Ambartsumyan, *Russ. J. Org. Chem.*, 2007, **43**, 1052.
38. M. Manoj and K. J. R. Prasad, *Synth. Commun.*, 2012, **42**, 434.
39. J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1958, 3368.
40. M. Sellstedt and F. Almqvist, *Org. Lett.*, 2011, **13**, 5278.
41. H. Wu, W. Lin, Y. Wan, H.-Q. Xin, D.-Q. Shi, Y.-H. Shi, R. Yuan, R.-C. Bo, and W. Yin, *J. Comb. Chem.*, 2010, **12**, 31.
42. F. Toda, K. Tada, and K. Hamai, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3207.
43. M. Manoj and K. J. R. Prasad, *J. Chem. Res.*, 2009, 485.
44. K. Okuma, T. Koga, Y. Suzuki, K. Horigami, N. Nagahora, K. Shioji, M. Fukuda, and M. Deshimaru, *Chem. Commun.*, 2014, **50**, 15525.
45. K. Okuma, A. Oba, R. Kuramoto, H. Iwashita, N. Nagahora, K. Shioji, R. Noguchi, and M. Fukuda, *Eur. J. Org. Chem.*, 2017, 6885.
46. H. Schultz, 'Benzodiazepines II,' Springer-Verlag, Berlin, 2012.
47. S. Michelini, G. B. Cassano, F. Frare, and G. Perugi, *Pharmacopsychiatry*, 1996, **29**, 127.
48. S. Pellow and S. E. File, *Neurosci. Biobehav. Rev.*, 1986, **10**, 221.
49. S. Solyom and I. Tarnawa, *Curr. Pharm. Des.*, 2002, **8**, 913.
50. S. Funar-Timofei, D. Ionescu, and T. Suzuki, *Toxicol. In Vitro*, 2010, **24**, 184.
51. K. Okuma, R. Itoyama, A. Sou, N. Nagahora, and K. Shioji, *Chem. Commun.*, 2012, **48**, 11145.
52. H. Yoshida, M. Watanabe, J. Ohshita, and A. Kunai, *Chem. Commun.*, 2005, 3292.
53. U. K. Tamber and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 5340.
54. K. Okuma, Y. Tanabe, N. Nagahora, and K. Shioji, *Bull. Chem. Soc. Jpn.*, 2015, **88**, 1064.
55. 'Tellurium in Organic Synthesis,' 2nd edn., ed. by N. Petragnani and H. A. Stefani, Academic Press, 2010, Chapter 3.2, pp. 40-47.
56. C. M. Rayner, 'Comprehensive Organic Functional Group Transformation,' ed. by A. R. Katritzky,

- O. Meth-Cohn, and C. W. Rees, 1995, Vol. 1,15, Pergamon, Oxford, UK (1995).
57. A. J. Katritzky and A. A. J. Boulton, 'Advances in Heterocyclic Chemistry,' Section II. B, Vol. 24, Academic Press, London, 1981, pp. 110-147.
58. T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, and F. S. Guziec, Jr., *J. Chem. Soc., Chem. Commun.*, 1975, 539.
59. T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, and F. S. Guziec, Jr., *J. Chem. Soc., Perkin Trans. 1*, 1976, 2079.
60. P. de Mayo, G. L. R. Petrašiūnas, and A. C. Weedon, *Tetrahedron Lett.*, 1978, 4621.
61. R. Okazaki, A. Ishii, and N. Inamoto, *J. Chem. Soc., Chem. Commun.*, 1983, 1429.
62. F. S. Guziec, Jr. and C. A. Moustakis, *J. Org. Chem.*, 1984, **49**, 189.
63. K. Okuma, J. Sakata, Y. Tachibana, T. Honda, and H. Ohta, *Tetrahedron Lett.*, 1987, **28**, 6649.
64. G. Erker, R. Hock, and R. Nolte, *J. Am. Chem. Soc.*, 1988, **110**, 624.
65. K. Okuma, K. Kojima, and H. Ohta, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1993, **80**, 259.
66. K. Okuma, K. Kojima, K. Oyama, K. Kubo, and K. Shioji, *Eur. J. Org. Chem.*, 2004, 820.
67. R. Huisgen, J. Penelle, G. Mloston, A. B. Padias, and H. K. Hall, Jr., *J. Am. Chem. Soc.*, 1992, **114**, 266.
68. M. Minoura, T. Kawashima, and R. Okazaki, *J. Am. Chem. Soc.*, 1993, **115**, 7019.
69. M. Minoura, T. Kawashima, N. Tokitoh, and R. Okazaki, *Tetrahedron*, 1997, **53**, 8138.
70. K. Okuma, K. Kubo, and Y. Yokomori, *Heterocycles*, 2003, **60**, 299.
71. R. Curtius, S. Hasnain, and J. Tayler, *J. Chem. Soc., Chem. Commun.*, 1968, 365.
72. P. Arsenyan, O. Pudova, and E. Lukevics, *Tetrahedron Lett.*, 2002, **43**, 4817.
73. E. Block, M. Birringer, R. DeOrazio, J. Fabian, R. S. Glass, C. Guo, C. He, E. Lorange, Q. Qian, T. B. Schroeder, Z. Shan, M. Thiruvazhi, G. S. Wilson, and X. Zhang, *J. Am. Chem. Soc.*, 2000, **122**, 5052.
74. K. Okuma, T. Izaki, K. Kubo, K. Shioji, and Y. Yokomori, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 1121.
75. K. Okuma, K. Nagakura, Y. Yakajima, K. Kubo, and K. Shioji, *Synthesis*, 2004, 1929.
76. K. Okuma and K. Munakata, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2011, **186**, 1196.
77. K. Okuma, S. Maekawa, S. Shibata, K. Shioji, T. Inoue, T. Kurisaki, H. Wakita, and Y. Yokomori, *Eur. J. Org. Chem.*, 2003, 3727.
78. K. Okuma, M. Koda, S. Maekawa, K. Shioji, T. Inoue, T. Kurisaki, H. Wakita, and Y. Yokomori, *Org. Biomol. Chem.*, 2006, **4**, 2745.
79. K. Okuma, S. Maekawa, Y. Nito, and K. Shioji, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1933.
80. K. Okuma, Y. Mori, T. Shigetomi, M. Tabuchi, K. Shioji, and Y. Yokomori, *Tetrahedron Lett.*, 2007, **48**, 8311.

81. K. Okuma, K. Munakata, H. Matsui, N. Nagahora, and K. Shioji, *Heterocycles*, 2014, **89**, 473.
82. K. Shimada M. Asahida, K. Takahashi, Y. Sato, S. Aoyagi, and C. Kabuto, *Chem. Lett.*, 1998, 513.
83. R. Steudel, *Chem. Rev.*, 2002, **102**, 3905.
84. T. Shigetomi, K. Okuma, and Y. Yokomori, *Tetrahedron Lett.*, 2008, **49**, 36.
85. 'Rodd's Chemistry of Carbon Compounds,' ed. by M. F. Ansell, Suppl., Vol. IIC, Elsevier, Amsterdam, 1974.
86. K. Okuma, T. Tsubota, M. Tabuchi, M. Kanto, N. Nagahora, K. Shioji, and Y. Yokomori, *Chem. Lett.*, 2010, **39**, 648.
87. K. Okuma, K. Munakata, T. Tsubota, M. Kanto, N. Nagahora, K. Shioji, and Y. Yokomori, *Tetrahedron*, 2012, **68**, 6211.
88. K. Okuma, S. Yahata, K. Kage, N. Nagahora, and K. Shioji, *Nat. Prod. Commun.*, 2016, 895.
89. P. R. Brooks, R. Bishop, J. A. Counter, and E. R. T. Tiekink, *J. Org. Chem.*, 1994, **59**, 1365.
90. K. Okuma, S. Yahata, K. Munakata, N. Nagahora, K. Shioji, R. Ishikawa, and Y. Yamada, *Chemistry Select*, 2016, **1**, 4652.
91. E. H. Braye, W. Hübel, and I. Caplier, *J. Am. Chem. Soc.*, 1961, **83**, 4406.
92. W. Mack, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 896.
93. G. He, L. Kang, W. Torres Delgado, O. Shynkaruk, M. J. Ferguson, R. McDonald, and E. Rivard, *J. Am. Chem. Soc.*, 2013, **135**, 5360.
94. K. Okuma, S. Yahata, N. Nagahora, and K. Shioji, *Chem. Lett.*, 2017, **46**, 405.



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