Studies on Low-valent Nb Catalyst for Selective Cycloaddition Reaction

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Studies on Low-valent Nb Catalyst for Selective Cycloaddition Reaction

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Studies on Low-valent Nb Catalyst for Selective Cycloaddition Reaction
（低原子価ニオブ触媒を用いた選択的環化付加反応の開発）

Abstract (概要)

20 世紀以降，有機金属錯体を触媒として利用した有機変換プロセスは目覚ましい発展を遂げている．触媒プロセスの利点としては，多大なエネルギーを要し，かつ多量の副生成物として廃棄物を産出し，高温や高圧環境を要求する環境高負荷型製造プロセスから脱却するための重要な役割を担うことできることである．

しかしながら，現用の金属触媒を利用した有機合成反応プロセスの多くは，パラジウム，白金やイリジウムなどの稀少貴金属を用いる必要がある．また稀少貴金属は化学工業の分野だけではなく，多岐にわたる分野から注目され利用されている元素でもある．そこで我々，触媒化学者に課せられた重要なテーマとして『稀少貴金属の代替化・低減化』等，金属資源の高効率利用があげられる．また近年では，代替金属として銅錯体や鉄錯体などコモンメタルを利用した有機変換反応の開発も活発におこなわれている．

以上の経緯より，申請者は代替金属の一つとして期待される前周期遷移金属化合物の一つであるニオブ錯体に着目し研究を開始した．なお本博士論文は 7 章から構成されている．第 1 章では低原子価ニオブを用い研究を開始した研究背景を述べる．第 2~4 章では従来，アルキンとアルケンとの反応から選択的な合成が困難とされていた 1,3-シクロヘキサジエン誘導体を 2 種類の低原子価ニオブ錯体を触媒として利用することにより成功し，それら反応の詳細について述べる．第 5, 6 章ではニオブ錯体を反応剤または触媒として利用したアルキンとニトリルとの環化付加反応によるピリミジンあるいはピリジン誘導体の選択的合成について述べる．第 7 章では総括について述べる．

【各章の要旨】

第１章 General Introduction (背景)

前周期遷移金属錯体を利用した有機変換反応は高周期遷移金属錯体を利用したそれと比べ特異的な反応性を示すため注目されている分野の一つである．とりわけ前周期低原子価金属錯体は還元能力が高く，その反応性を利用した有機変換反応が多く報告されている．しかしながら，その報告例の多くはチタンやジルコニウムに代表される周期表第 4 族の前周期低原子価金属化合物を利用しており，アルキンとの反応によって得られる金属－アルキン錯体と求電子剤との反応を対象にしている．このように前周期低原子価金属化合物は有用な有機変換ツールである．しかしながら問題点も存在し，(i)等量以上の金属試薬を必要とする化学量論反応であること，(ii)熱的に不安定な金属種が多く，室温より低温以下で反応させるため合成反応上の強い制約があること，などが挙げられる．

申請者は上記の研究背景を踏まえ，熱的に安定な前周期低原子価金属化合物の一つである周期表第 5 族のニオブ(Nb)化合物を用い以下の章に示す研究成果を得ることに成功した．

第２章 $NbCl_3$-catalyzed Intermolcular [2+2+2] Cycloaddition of Alkynes and α,ω-Dienes: Highly Chemo- and Regioselective Formation of 5-ω-Alkenyl-1,4-substituted-1,3-cyclohexadiene Derivatives
(低原子価ニオブ触媒を用いた末端アルキンと α,ω - ジエンとの環化付加反応による 1,3-シクロヘキサジエン誘導体の合成)

1,3-シクロヘキサジエン誘導体は Diels-Alder 反応の原料または耐熱性に優れたシクロヘキサジエンポリマーのモノマー原料として有用である．また遷移金属触媒を用いた 2 分子のアルキンと 1 分子のアルケンとの分子間[2+2+2]環化付加反応は 1,3-シクロヘキサジエン誘導体を合成する手法としてアトムエコノミーな合成法の 1 つとして挙げられる．しかしながら，これら報告例は非常に限られている．報告例が少ない要因としては, アルキンの環化三量化反応が優先するため 1,3-シクロヘキサジエン誘導体を選択的に合成することが困難であることが挙げられる．

本章では $NbCl_3$(DME)触媒を利用することにより，末端アルキンと α,ω-ジエンとの分子間環化付加反応が進行し，5-ω-アルケニル-1,3-シクロヘキサジエン誘導体が選択的に得られることを見出した．本反応では様々な α,ω-ジエンを反応に適用可能であり，対応する生成物を高収率で与えた．なお本章では本反応における反応条件の検討，反応基質の適用範囲の検討等の詳細について述べる．

第３章 $NbCl_3$-catalyzed Three-component [2+2+2] Cycloaddition Reaction of Terminal Alkynes, Internal Alkynes, and Alkenes to 1,3,4,5-Tetrasubstituted 1,3-Cyclohexadienes
(低原子価ニオブ触媒を用いた末端アルキンと内部アルキンと末端アルケンとの三成分環化付加反応による四置換体 1,3-シクロヘキサジエン誘導体の合成)

入手容易な単純化合物を用いた分子間環化付加反応は得られる化合物に様々な置換基を導入できるため魅力的な反応である．例えば異なる 3 種類の出発原料から[2+2+2]環化付加反応によって得られる化合物は異性体を含めると 10 種類以上にもなる．その中から 1 つの化合物を選択的に合成することは非常に困難である．また多成分分子間環化付加反応の例としては，低原子価ジルコニウム錯体を利用した異なる 3 種類の内部アルキンを用い, 多置換体ベンゼン誘導体を合成する反応が報告されている．しかしながら目的化合物を合成するためには多段階を要し，量論量以上の金属を必要としていた．

本章では，$NbCl_3$(DME)触媒を利用することにより，末端アルキン，内部アルキンおよび末端アルケンとの三成分[2+2+2]環化付加反応が進行し，四置換体 1,3-シクロヘキサジエン誘導体が選択的に得られることを見出した. 本反応では様々な末端アルキン, 内部アルキンおよび末端アルケンが適用可能であり，対応する生成物を高収率で与えた．なお本章では本反応における反応条件の検討，反応基質の適用範囲の検討等の詳細ににについて述べる．

第４章 Active Low-valent Niobium Catalysts from $NbCl_5$ and Hydrosilanes for Selective Intermolecular Cycloadditions
(五塩化ニオブとヒドロシランから発生する低原子価ニオブ触媒を利用した高選択的 1,3-シクロヘキサジエン誘導体の合成)

従来，反応性の高い前周期低原子価金属化合物は，還元剤として Grignard 試薬，*n*-ブチルリチウムや金属亜鉛といった反応性の高い金属試薬を用い合成されていた．低原子価ニオブ錯体の一つである $NbCl_3$(DME)錯体も例外ではなく，低原子価前駆体錯体として $NbCl_5$ を用い，還元剤として水素化トリブチルスズ(Bu_3SnH)を用い合成を行っていた．

本章では還元剤としてヒドロシラン化合物を用い $NbCl_5$ から低原子価ニオブ種が発生することを見出した．またそれを触媒として用いることにより，末端アルキンとアルケンとの環化付加反応が進行することを見出した．本反応は様々なアルケンが適用可能であり，対応する生成物を高収率で与えた．なお本章では本反応における反応条件の検討，反応基質の適用範囲の検討，低原子価ニオブ種の発生および反応機構に関わる実験の詳細にについて述べる．

第５章 Strategy for the Synthesis of Pyrimidine Derivatives: $NbCl_5$-mediated Cycloaddition of Alkynes and Nitriles

(五塩化ニオブを用いたアルキンとニトリルとの環化付加反応によるピリミジン誘導体の合成)

ピリミジン誘導体は天然物，生理活性化合物に含まれる重要な化合物である．それらのアトムエコノミーな合成法の一つとして 1 分子のアルキンと 2 分子のニトリルとの環化付加反応があげられる．

本章では，量論量の $NbCl_5$ を用いアルキンとニトリルとを反応させることにより，ピリミジン誘導体が得られることを見出した．本反応は様々なアルキン，芳香族ニトリルが適用可能であり，対応する生成物を選択的に与えた．なお本章では本反応における反応条件の検討, 反応基質の適用範囲の検討等の詳細について述べる．

第６章 Low-valent Niobium-catalyzed Intermolecular [2+2+2] Cycloaddition of *tert*-Butylacetylene and Arylnitriles to Form 2,3,6-Trisubstituted-pyridine Derivatives

(五塩化ニオブと亜鉛とアルコキシシランから発生する低原子価ニオブを触媒として利用した末端アルキンとニトリルとの環化付加反応によるピリジン誘導体の合成)

ピリジン誘導体は天然物，生理活性化合物に含まれる重要な化合物である．従って，ピリジン誘導体の効率的な合成法はこれまで多く報告されている．その中でも遷移金属触媒を用いたアルキンとニトリルとの環化付加反応による合成は様々な遷移金属錯体を利用することにより達成されているが，触媒化された例は後周期遷移金属化合物に限定されていた．一方，前周期遷移金属錯体を利用した反応の全てが触媒反応ではなく，量論反応として報告されている．

本章では $NbCl_5$ と亜鉛とアルコキシシランから発生する低原子価ニオブを用いることにより，末端アルキンとニトリルとの環化付加反応が進行し，ピリジン誘導体が触媒的に得られることを見出した．本反応では様々なニトリル化合物が適用可能であり，対応する生成物を良好な収率で与えた．なお本章では本反応における反応条件の検討, 反応基質の適用範囲の検討, 反応機構に関する証明実験等の詳細について述べる．

第７章 General Conclusion (総括)

本研究で得られた結果を総括する．

以上

Contents

Chapter 1
General Introduction

Background

Rare metals are used in a wide diversity of end-use applications, from capacitors electronics and metallic cathodes for rechargeable batteries to photovoltaic solar cell and semiconductor materials. In addition, some rare metals are used in chemical industry. We also utilize rare metals, in particular Pd, Ir, Ru, Pt, and etc., for most catalytic reaction. As a result, dwindling rare metals have been acknowledged as a problem. Therefore, I have a need to make effective use resource efficiency for future society.

Low-valent early transition-metal

Low-valent early transition-metal mediated or catalyzed organic transformation is intriguing owing to the inherent capability of these metals as reductants for activation of unsaturated compounds.[1] To date, reactions with Ti(II),[2] Zr(II),[3] Ta(III),[4] and Nb(III)[5] have been intensively explored. Conventionally, these low-valent metals were prepared by reduction using harsh reducing agents such as elemental metals (Na, Li, Zn), alkyllithiums, Grignard reagents, or $LiAlH_4$.[2-5] In general, these low-valent early transition-metal species (Ti(II), Zr(II)) are thermally unstable, and their preparation and utilization should be performed at low temperature, which hampered their attractiveness for use in catalytic reactions.

Synthesis of low-valent Nb(III) complex, $NbCl_3$(DME)

In 1987, Pedersen and co-workers reported the preparation of $NbCl_3$(DME), a thermally-stable low-valent early transition-metal complex, by the treatment of $NbCl_5$ with Bu_3SnH in DME (Scheme 1).[6] This complex is currently commercially available and has been utilized as both reagent and catalyst in organic transformations.

$$NbCl_5 + 2Bu_3SnH \xrightarrow[-78\ ^oC]{DME} NbCl_3(DME) + 2Bu_3SnCl + H_2$$

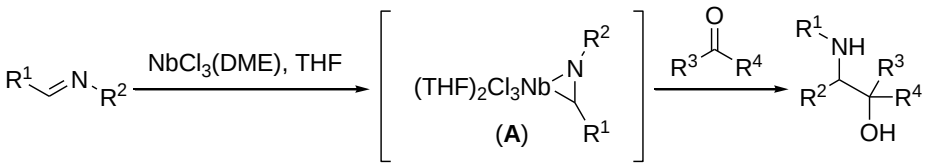
Scheme 1. Preparation of $NbCl_3$(DME) from reaction of $NbCl_5$ wtih Bu_3SnH in DME.

Applications of organic synthesis reaction with stoichiometric amount of Nb(III)

The application of low-valent early transition metals as two electron reductants in organic systhesis has centered around titanium and zirconium complexes. I have been interested in using $NbCl_3L_n$ reagents with anticipation that such species should exhibit markedly different reaction

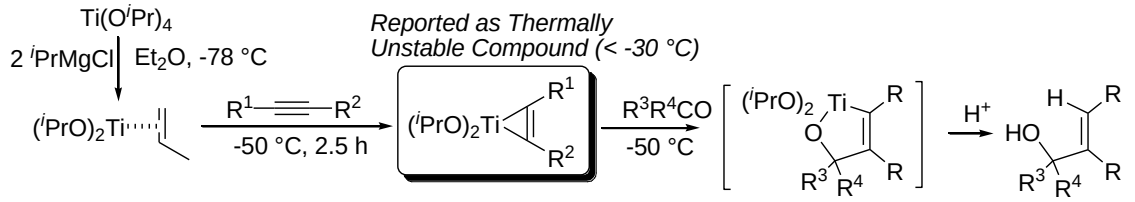
chemistry from the group IV metallocenes. These differences would arise from the enhanced Lewis acidity of the niobium-chloride complexes and the potential for substitution of the choloride with other ligands.

Pedersen has reported $NbCl_3$(DME) may be prepared in large quantitites, and it is a useful reagent for a variety of organic transformations, such as the cross coupling of imines by using niobium reagent, $NbCl_3$(DME) (Scheme 2).[6] Desired products were obtained by the formation of Nb-imine complex (**A**).



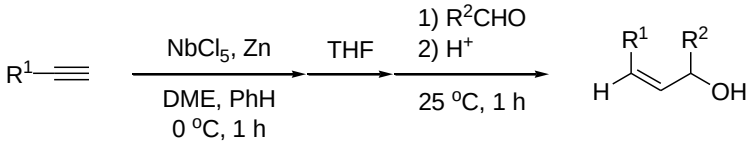
Scheme 2. Transformation of imines mediated by stoichiometric amount of $NbCl_3$(DME).

Low-valent early transition-metal halides are known to react with alkyne to give alkyne complexes. And these complexes proposed can be considered as a C, C-dianion equivalent. Therefore, alkyne complexes of low-valent early transition-metal are useful synthetic reagents, and reactions with various electrophiles have been investigated and developed. In particular, Ti(II)-alkyne complexes have been intensively studied. However, these complexes must be generated in situ from Ti(IV) with a reducing reagents. Moreover, the resulting Ti(II)-alkyne complexes are thermally unstable and can not be utilized in further synthetic reactions which are carried out below -30 °C (Scheme 3).[2]



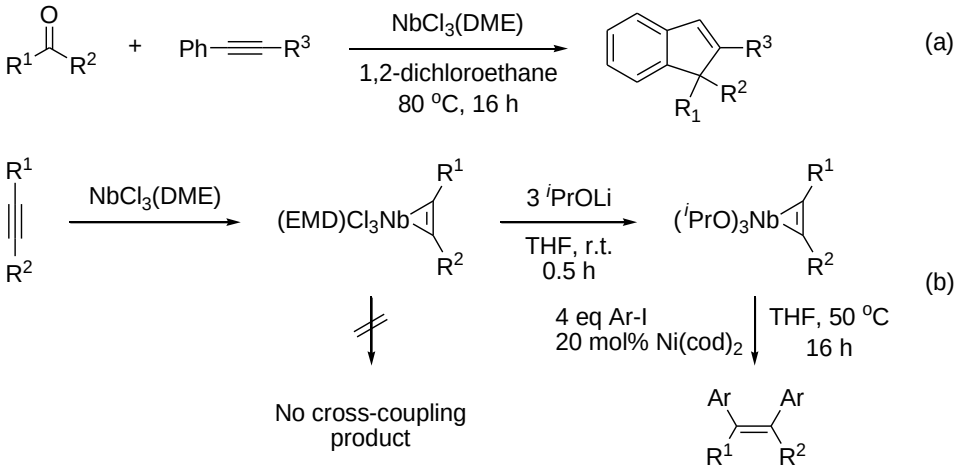
Scheme 3. Thermally unstable Ti(II)-alkyne complexes from Ti(IV) and ^{i}PrMgCl.

In contrast, Nb(III) compound is thermally stable complex. While only a limited number of synthetic applications of the Nb(III) reagents have been investigated.[5] Takai and co-workers reported that synthesis of allyl alcohol derivatives from alkynes and aldehydes by using Nb(III) (generated in situ from $NbCl_5$ and Zn) (Scheme 4).[5a]



Scheme 4. Synthesis of allyl alcohol derives from Nb-alkyne complexes and aldehydes.

Tsuji, Obora, and co-workers reported $NbCl_3$(DME)-mediated synthesis of 1,1,2-trisubstitutd 1*H*-indenes from aliphatic ketones and aryl-substituted internal alkynes (Scheme 5-a),[7a] and Nickel-catalyzed cross-coupling reaction of Nb(III)-alkyne complexes with aryl iodides (Scheme 5-b).[7b]



Scheme 5. Reaction of Nb(III)-alkyne complexes with electrophiles.

These reactions were performed by using stoichiometric amount of Nb(III). So, I should develop reactions with catalytic amount of Nb(III).

Catalytic reactions using low-valent transition metals

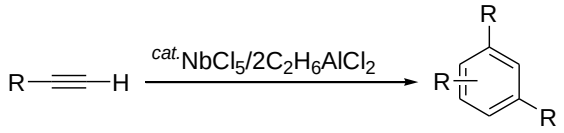
Low-valent transition-metal possesses more electron on metal center than high-valent transition-metal. Ru(0) compounds are known as one of low-valent transition-metal. For example, Ru(0)-catalyzed cycloaddition with alkynes initiates oxidative cycloaddition of two alkynes molecules on Ru(0) to form rutenacyclopentadiene complexes. Thereafter Ru-cyclopentadiene complexes were reacted one alkyne molecule, and then produces corresponding desired benzene derivatives. Thus, catalytic reactions with low-valent late transition-meatal have been developed.

On the other hand, the use of low-valent early transition-metal as catalysts is unexplored field.

Catalytic reactions using low-valent early transition metals

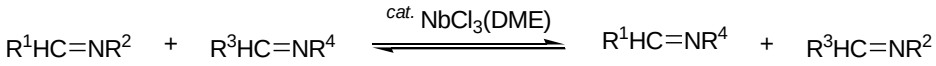
To date, some catalytic reactions employing early transition-metal have been reported.

In 1991, Du Toit and co-workers reported a low-valent niobium-catalyzed cyclotrimerization of terminal alkynes (Scheme 6).[8] When $NbCl_5$ was used as catalyst in the reaction, even though terminal alkyne was evidently converted during the course of the reaction, almost none of the desired benzene derivatives were observed. In this reaction, I probably anticipate that catalytic active species is low-valent niobium from $NbCl_5$ and $C_2H_6AlCl_2$.



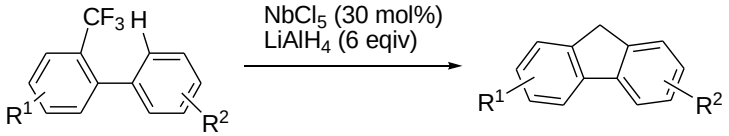
Scheme 6. Cyclotrimerizaton of terminal alkynes by low-valent niobium catalyst

Bruno and co-workers reported the use of niobium(III) and niobium(V) compounds in catalytic imine metathesis (Scheme 7).[9] The niobium reagents $NbCl_3$(DME) and mer-(DME)Cl_3Nb=NPh serve as effective catalysts or precatalysts in imine metathesis reactions with a variety of aldimines.



Scheme 7. $NbCl_3$(DME)-Catalyzed imine metathesis reaction

Fuchibe and co-workers reported a low-valent niobium generated *in situ* from $NbCl_5$ and $LiAlH_4$ served as catalyst for the reductive cleavage reactions of C-F and C-H bonds (Scheme 8).[10] These reactions has contributed widely toward the development of cleavage of unactivated bonds.



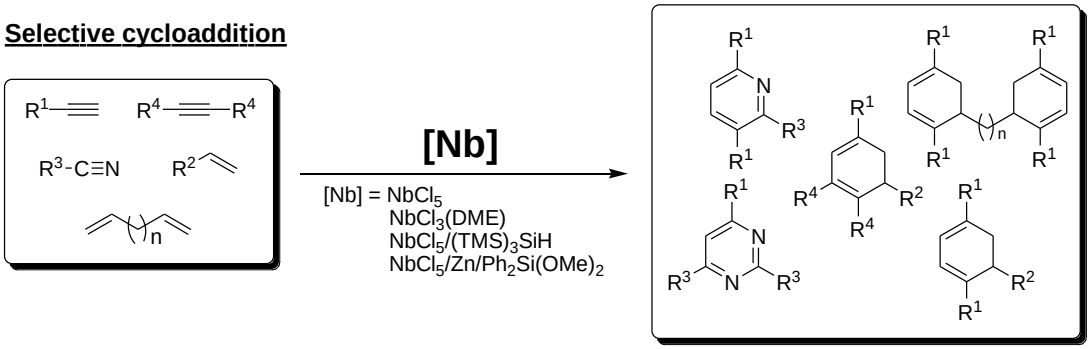
Scheme 8. Low-valent Nb catalyzed reductive cleavage reaction of C-F bonds

Obora, Ishii, and Takeshita previously reported $NbCl_3$(DME)-catalyzed [2 + 2 + 2] cycloaddition of alkynes with alkenes to 1,3-cyclohexadiene derivatives (Scheme 9).[11] The reaction would proceed as follows; (i) oxidative cycloaddition of terminal alkynes to Nb(III) to form niobacyclopentadiene intermediate; (ii)Diels-Alder reaction of niobacyclopentadiene intermediate with alkenes followed by reductive elimination of Nb to give desired products.

Scheme 9. Nb(III)-Catalyzed intermolecular cycloaddition of alkynes and alkenes

Brief overview of the present thesis

On the basis of these knowledge and information, I aniticipated that the low-valent niobioum complex would take a role as various metallacycle intermediates to get various cyclic products. The present thesis describes Nb-mediated selective cycloaddition reaction of alkynes with alkenes or nitriles to form 1,3-cyclohexadienes, pyrimidines, or pyridines (Scheme 10).[12-16]



Scheme 10. Nb complex-mediated or -catalyzed intermolecular cycloaddition of unsaturated compounds

In Chapter 2, highly chemoselective cycloaddition of terminal alkynes and α,ω-dienes, catalyzed by $NbCl_3$(DME) complex, leading to 5-ω-alkenyl-1,3-cyclohexadienes is described.[12] The present reaction provides a novel protocol for the selective formation of 5-ω-alkenyl-substituted-1,3-cyclohexadiene derivatives, which also enables the conversion to 5-ω-acetyl-substituted 1,3-cyclohexadiene derivatives.

In Chapter 3, I described $NbCl_3$(DME)-catalyzed three-component [2 + 2 + 2] cycloaddition of terminal alkynes, internal alkynes, and terminal alkenes, leading to 1,3,4,5-tetrasubstituted 1,3-cyclohexadienes in excellent yields with high chemo- and regioselectivity.[13] This reaction provides an unprecedented, selective, and atom-economical methodology for the formation of tetrasubstituted 1,3-cyclohexadienes from three different simple unsaturated compounds via intermolecular [2 + 2 + 2] cycloaddition.

In Chapter 4, I described a simple and nontoxic method for the generation of novel low-valent niobium species from $NbCl_5$, using hydrosilanes as reducing agents.[14] This novel $NbCl_5$/hydrosilane catalyst system surpasses the existing $NbCl_3$(DME) catalyst with regard to both catalytic activity and

selectivity in the intermolecular [2 + 2 + 2] cycloadditions of alkynes and alkenes

In Chapter 5, I found that intermolecular cycloadditions of alkynes (terminal alkynes and internal alkynes) with aryl nitriles were successfully achieved, using an $NbCl_5$ complex, to give substituted pyrimidine derivatives in high yields with excellent chemo- and regioselectivity.[15]

In Chapter 6, I described a catalytic system based on low-valent niobium has been developed, consisting of $NbCl_5$, Zn, and an alkoxysilane.[16] This combination has been shown to be an efficient catalyst for the synthesis of pyridine derivatives from the intermolecular cycloaddition of alkynes and nitriles via a niobacyclopentadiene intermediate.

References

(1) (a) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev*. **2000**, *100*, 2835. (b) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755. (c) Negishii, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (d) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev*. **2000**, 100, 2835. (e) Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 319.

(2) (a) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696. (b) Kawaji, T.; Shohji, N.; Miyashita, K.; Okamoto, S. *Chem. Commun*. **2011**, *47*, 7857. (c) Rosenthal, U.; Burlaakov, V. V.; Bach, M. A.; Beweries, T. *Chem. Soc. Rev*. **2007**, *36*, 719. (d) Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett*. **2003**, *5*, 2145. (e) Lysenko, I. L.; Hyung, K. K.; Lee, G.; Cha, J. K. *J. Am. Chem. Soc*. **2008**, *130*, 15997. (f) Tarselli, M. A.; Micalizio, G. C. *Org. Lett*. **2009**, *11*, 4596. (g) Hanamoto, T.; Yamada, K. *J. Org. Chem*. **2009**, *74*, 7559. (h) Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc*. **1993**, *115*, 1581. (i) Johnson, E. S.; Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 7685.

(3) (a) Takahashi, T.; Tsai, F. -Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc*. **1999**, *121*, 11093. (b) Kanno, K.; Igarashi, E.; Zhou, L.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc*. **2008**, *130*, 5624. (c) Wang, G.; Negishi, E. *Eur. J. Org. Chem*. **2009**, 1679. (d) Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc*. **2007**, *129*, 12634. (e) Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burlakov, V. V.; Rosenthal, U. *Synlett* **1996**, 118.

(4) (a) Shimizu, H.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 7593. (b) Oshiki, T.; Tanaka, K.; Yamada, J.; Ishiyama, T.; Kataoka, Y.; Mashima, K.; Tani, K.; Takai, K. *Organometallics* **2003**, *22*, 464. (c) Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett*. **1995**, 851. (d) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem. Int. Ed*. **2002**, *41*, 1389. (e) Brennessel, W. W.; Ellis, J. E.; Pomije, M. K.; Sussman, V. J.; Urnezius, E.; Young, V. G., Jr. *J. Am. Chem. Soc*. **2002**, *124*, 10258.

(5) (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem*. **1992**, *57*, 1973. (b) Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc*. **2006**, *128*, 1434. (c) Arai, S.; Takita, S.; Nishida, A. *Eur. J. Org. Chem*. **2005**, 5262. (d) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett*. **1990**, *31*, 365. (e) Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, K. *Tetrahedron Lett*. **1990**, *31*, 369. (f) Oshiki, T.; Nomoto, H.; Tanaka, K.; Takai, K. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 1009.

(6) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc*. **1987**, *109*, 6551.

(7) (a) Obora, Y.; Kimura, M.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2005**, 901. (b) Obora, Y.; Kimura, M.; Ohtake, T.; Tokunaga, M.; Tsuji, *Organometallics* **2006**, *25*, 2006.

(8) Du Plessis, J. A. K.; Viljoen, J. S.; Du Toit, C. J. *J. Mol. Catal.* **1991**, *64*, 269.

(9) J. W. Bruno, X. J. Li, *Organometallics* **2000**, *19*, 4672.

(10) (a) Fuchibe, K.; Mitomi, K.; Suzuki, R.; Akiyama, T. *Chem. Asian J*. **2008**, *3*, 261. (b) Fuchibe,

K.; Oshima, Y.; Mitomi, K.; Akiyama, T. *Org. Lett.* **2007**, *9*, 1497. (c) Fuchibe, K.; Mitomi, K.; Akiyama, T. *Chem. Lett*. **2007**, *36*, 24. (d) Fuchibe, K.; Akiyama, T.; *J. Am. Chem. Soc*. **2006**, *128*, 1434. (e) Fuchibe, K.; Keneko, T.; Mori, K.; Akiyama, T. *Angew. Chem. Int. Ed*. **2009**, *48*, 8070.

(11) Obora, Y.; Takeshita, K.; Ishii, Y. *Org. Biomol. Chem.* **2009**, *7*, 428.

(12) Obora, Y.; Satoh, Y.; Ishii, Y. *J. Org. Chem*. **2010**, *75*, 6047.

(13) Satoh, Y.; Obora, Y. *Org. Lett*. **2011**, *13*, 2568.

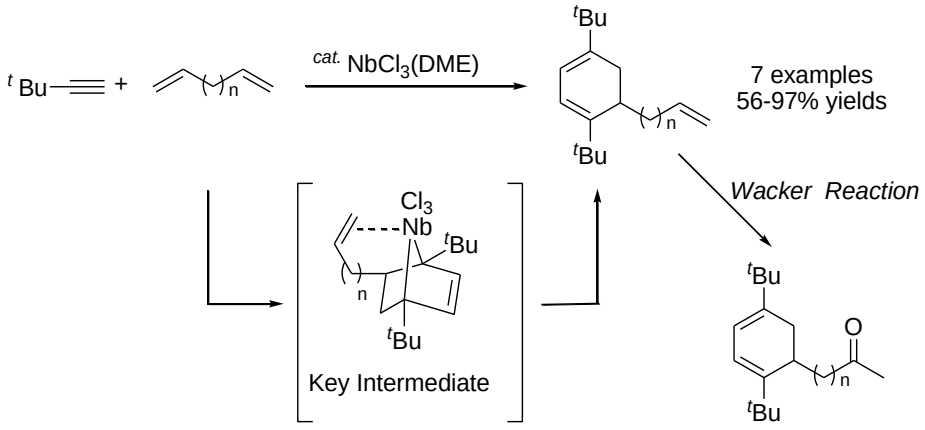
(14) Satoh, Y.; Obora, Y. *J. Org. Chem*. **2011**, *76*, 8569.

(15) Satoh, Y.; Yasuda, K.; Obora, Y. *Organometallics* **2012**, *31*, 5235.

(16) Satoh, Y.; Obora, Y. *J. Org. Chem*. **2013**, *78*, 7771.

Chapter 2

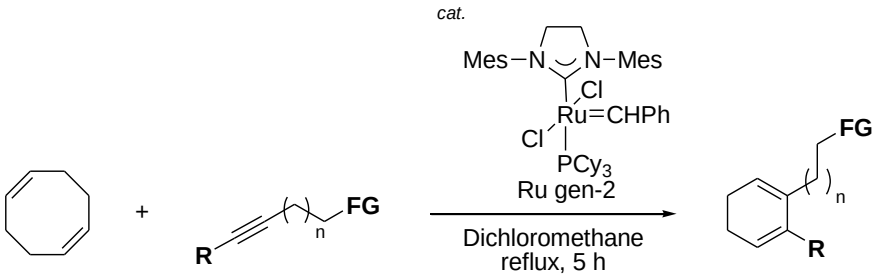
$NbCl_3$-catalyzed Intermolecular [2 + 2 + 2] Cycloaddition of Alkynes and α,ω-Dienes: Highly Chemo- and Regioselective Formation of 5-ω-Alkenyl-1,4-substituted-1,3-cyclohexadiene Derivatives



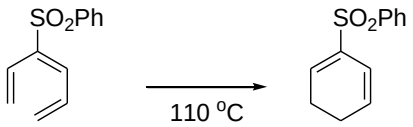
2-1. Introduction

1,3-Cyclohexadiene derivatives are an important class of compounds and are widely employed in organic synthesis.[1] In addition, these compounds have been utilized as monomers for good transparency and heat resistance polymers.[2] Therefore, various methods for the synthesis of substituted 1,3-cyclohexadienes have been investigated.[3] Recent methods to the access of these compounds include tandem diene-alkyne metathesis (Scheme 2-1)[4] and 1,6-electrocyclic reaction of 1,3,5-hexatrienes (Scheme 2-1).[5]

Diver (ref 4)



Brandänge (ref 5)

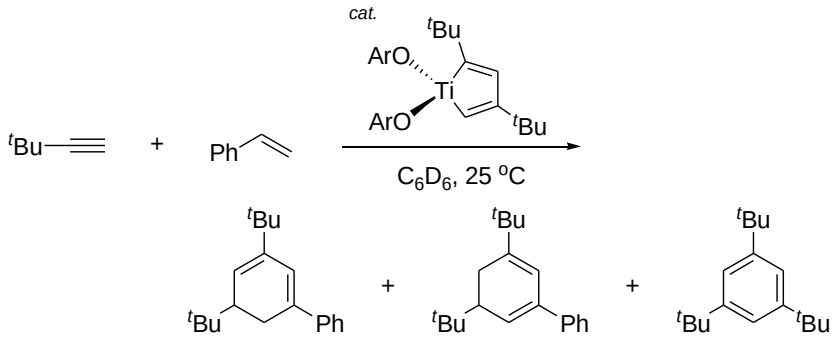


Scheme 2-1 Synthesis of 1,3-cyclohexadiene

In contrast, transition-metal-catalyzed [2 + 2 + 2] intermolecular cycloaddition by the reaction of two alkyne molecules and one alkene is one of the simplest and most atom-economical methods for preparing 1,3-cyclohexadienes. However, this methodology mainly leads to the cyclotrimerization of alkynes[6,7] in preference to the desired cross-cyclotrimerization between alkynes and alkenes. Therefore, only a limited amount of work has been reported so far.[8,9] As a pioneering work for this synthetic protocol, Rothwell and co-workers reported the intermolecular cycloaddition of alkynes and alkenes leading to 1,3-cyclohexadienes by titanacyclopentadiene catalyst (Scheme 2-2).[8] However, this method generally affords 1,3-cyclohexadienes in unsatisfactory yields and selectivities. In addition, this reaction pathway typically includes an isomerization step through 1,5-hydrogen shift of thermally unstable low-valent titanium species such as the titananorbornene intermediate.[8] Alternatively, $NbCl_3$(DME) is a thermally stable low-valent early transition metal complex that shows high reactivity in several stoichiometric and catalytic reactions with alkynes.[10-13] As a preliminary attempt, my group reported $NbCl_3$(DME)-catalyzed intermolecular cycloaddition of 1-alkynes and 1-alkenes to 1,3-cyclohexadienes (Scheme 2-3).[14] However, this approach is still problematic with regard to access of the desired 1,3-cyclohexadiene derivatives in high yield and

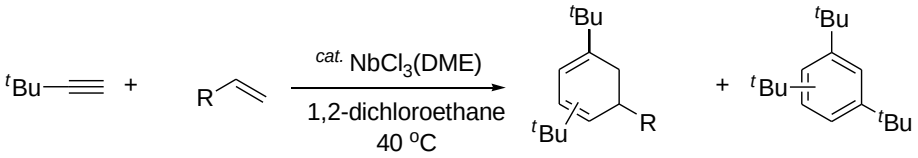
selectivity, which generally gives a cyclotrimerization adducts of alkyne in substantial yields.[14] Therefore, the development of a novel and efficient methodology for chemo- and regioselective formation of 1,3-cyclohexadienes by [2 + 2 + 2] cycloaddition of alkenes and alkynes remains an unsoluble problem and a challenging target.

Rothwell (ref 8)



Scheme 2-2. Synthesis of 1,3-cyclohexadienes by cycloaddition reactions catalyzed by Ti-complex

Obora (ref 14)

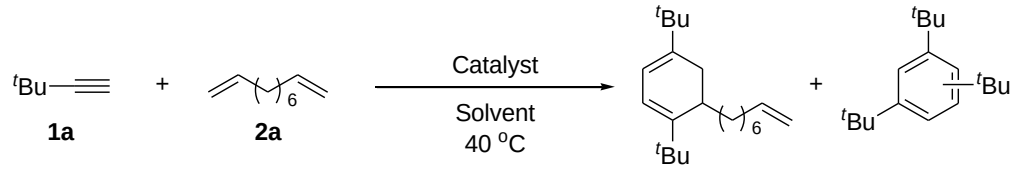


Scheme 2-3. Synthesis of 1,3-cyclohexadienes by cycloaddition reactions catalyzed by Nb-complex

2-2. Result and Discussion

tert-Butylacetylene (**1a**) and 1,9-decadiene (**2a**) were chosen as model substrates and the reaction was carried out under various conditions (Table 2-1). For instance, a mixture of **1a** (2 mmol) and **2a** (4 mmol) in 1,2-dichloroethane (1 mL) was allowed to react under the influence of a catalytic amount of $NbCl_3$(DME) (0.2 mmol, 10 mol %) at 40 °C for 4 h, giving 1,4-di-*tert*-butyl-5-(7-heptenyl)-1,3-cyclohexadiene (**3a**) in 97% yield (entry 1). In contrast to the previous paper,[14] the reaction proceeded highly chemo- and regioselectively to afford 1,4,5-trisubstituted-1,3-cyclohexadiene (**3a**) almost exclusively. In this reaction, only a negligible amount of tri-*tert*-butylbenzenes (**4a**) was detected by GC (entry 1). The regiostructure of the 1,4,5-substituted cycloaddition product (**3a**) was characterized by ^{1}H and ^{13}C-NMR, which resonances were assigned by means of 2D HMQC and HMBC spectroscopies.

Table 2-1 $NbCl_3$(DME)-catalyzed reaction of *tert*-butyl acetylene (**1a**) with 1,9-decadiene (**2a**).[a]



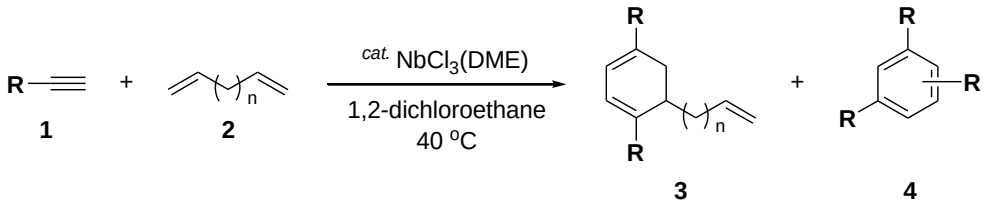
			Yield (%) [b]	
Entry	Catalyst	Solvent	**3a**	**4a**
1	$NbCl_3$(DME)	1,2-dichloroethane	97 [81] (92)	trace
2[c]	$NbCl_3$(DME)	1,2-dichloroethane	65 (90)	7
3[d]	$NbCl_3$(DME)	1,2-dichloroethane	27 (94)	9
4	$NbCl_3$(DME)	1,4-dichlorobutane	83 (91)	trace
5	$NbCl_3$(DME)	THF	9 (46)	26
6	$NbCl_3$(DME)	DME	n.d.[e]	n.d.[e]
7	$NbCl_3$(DME)	Toluene	n.d.[e]	n.d.[e]
8	$TaCl_3$(DME)	1,2-dichloroethane	n.d.[e]	n.d.[e]
9	$NbCl_5$	1,2-dichloroethane	n.d.[e,f]	n.d.[e,,f]
10[g]	Cp_2NbCl_2	1,2-dichloroethane	n.d.[e]	n.d.[e]
11[g]	$VCl_3(THF)_3$	1,2-dichloroethane	n.d.[e]	n.d.[e]

(a) **1a** (2 mmol) was allowed to react with **2a** (4 mmol) in the presence of catalyst (0.2 mmol, 10 mol%based on **1a**) in solvent (1 mL) at 40 °C for 2 h. (b) Yields were determined by GC based on **1a** used. The number in square bracket shows isolated yield. The numbers in parentheses show the selectivity (%) of 1,4,5-substituted adduct. The regiochemistry of other isomers was not determined. (c) **1a** (2 mmol) and **2a** (2 mmol) were used. (d) **1a** (2 mmol) and **2a** (1 mmol) were used. (e) Not detected by GC. (f) The substrates **1a** and **2a** were converted thoroughly and an intractable mixture of unidentified oligomerization products was obtained.

The yield of **3a** was influenced by the ratio of the substrate **1a** to **2a** and the best yield was obtained when the reaction of **1a** and **2a** was carried out with 1:2 molar ratio (entry 1). As the amount of **2a** was reduced, the yield of **3a** was lowered (entries 2 and 3). However, it is noteworthy that the reaction was exclusively subjected to react only the single alkene side of α,ω-dienes with the alkyne and **3a** was the sole cross-cycloaddition product. The reaction was greatly affected by the solvent employed and halogenated solvents such as 1,2-dichloroethane and 1,4-dichlorobutane realized high selectivity of **3a** (entries 1 and 4). On the other hand, the use of other solvents such as THF, toluene, and DME resulted in a decrease in the yields of **3a** (entries 5-7). As for the catalyst

precursor of this reaction, a low-valent Nb(III) complex, $NbCl_3$(DME), is highly efficient. When a low-valent Ta(III) analogue, $TaCl_3$(DME), was used as a catalyst, even though **1a** was evidently converted during the reaction course, no desired 1,3-cyclohexadiene adduct was produced at all (entry 8). Other Nb(IV), Nb(V), and V(III) complexes such as $NbCl_5$, Cp_2NbCl_2, and $VCl_3(THF)_3$ were totally ineffective catalysts for the formation of cycloaddition products (entries 9-11).

Table 2-2 $NbCl_3$(DME)-catalyzed reaction of terminal alkynes (**1**) and α,ω-dienes (**2**)[a]



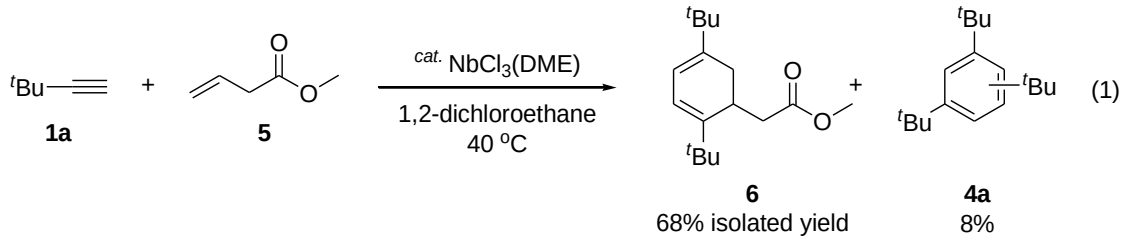
			Yield (%)[b]	
Entry	Alkyne (**1**) R	α,ω-Dienes (**2**)	**3**	**4**
1	*t*-Bu (**1a**)	1,9-Decadiene (*n*=6) (**2a**)	97 [81] (62) (**3b**)	trace
2	*t*-Bu (**1a**)	1,5-Hexadiene (*n*=2) (**2b**)	78 [63] (86) (**3b**)	6 (**4a**)
3	*t*-Bu (**1a**)	1,7-Octadiene (*n*=4) (**2c**)	84 [64] (91) (**3c**)	trace
4	*t*-Bu (**1a**)	1,11-Dodecadiens (*n*=8) (**2d**)	73 [64] (95) (**3d**)	trace
5	*t*-Bu (**1a**)	1,13-Tetradecadiene (*n*=10) (**2e**)	56 [36] (>99) (**3e**)	n.d.
6	Me_3Si (**1b**)	**2a**	[65] (>99) (**3f**)	18 (**4b**)
7	*n*-Bu (**1c**)	**2a**	n.d.	64 (**4c**)
8	Ph (**1d**)	**2a**	trace	48 (**4d**)

(a) **1** (2 mmol) was allowed to react with **2** (4 mmol) in the presence of $NbCl_3$(DME) (0.2 mmol, 10 mol% based on **1**) in 1,2-dichloroethane (1 mL) at 40 °C for 2 h. (b) Yields were determined by GC based on **1** used. The numbers in square brackets show isolated yields. The numbers in parentheses show the selectivity (%) of 1,4,5-substituted adducts. The regiochemistry of the other isomers was not determined.

Using the optimized condition is shown in Table 2-1, entry 1, reactions of various 1-alkynes (**1a-d**) with α,ω-dienes (**2b-e**) were examined (Table 2-2). The yields of the 1,3-cyclohexadiene products (**3**) were somewhat influenced by the alkyl chain length of the α,ω-dienes (**2**) and the reaction of **1a** with various α,ω-dienes (**2**) produced the corresponding 5-ω-alkenyl-1,4-di-*tert*-butyl-1,3-cyclohexadiene derivatives (**3b-e**) in good to excellent yields (56-97%) with high to excellent chemo- and regioselectivity (86-99%) (entries 1-5). In this reaction, the yield and selectivity of the reaction were greatly affected by the bulkiness and electronic nature of alkyne substituents. The best yield and selectivity for the formation of **3a** was achieved when the reaction was carried out with *tert*-butylacetylene (**1a**). On the other hand, the reaction of

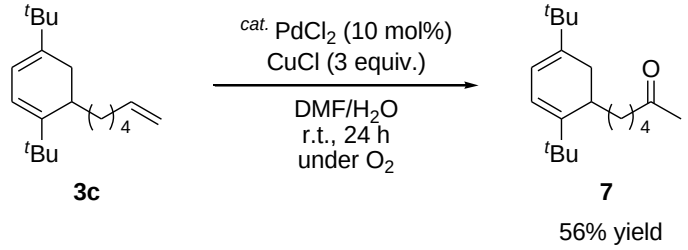
trimethylsilylacetylene (**1b**) with **2a** led to the mixture of the corresponding intermolecular cycloaddition products (**3f**) and the alkyne cyclotrimerization products (**4b**) (entry 6). Alkynes having less bulky substituents such as 1-hexyne (**1c**) and phenylacetylene (**1d**) resulted in alkyne cyclotrimerization products (**4c**-**d**) as major adducts (entries 7 and 8).

The reaction can be extended to the formation of ω-acetoxysubstituted 1,3-cyclohexadiene (eq 1). For eznmple, the reaction of **1a** (2 mmol) with methyl but-3-enoate (**5**) (2 mmol) under optimized conditions afforded **6** in 68% yield as a single regioisomer (1,4,5-adduct) along with the formation of **4a** in 8% yield (eq 1).



(1)

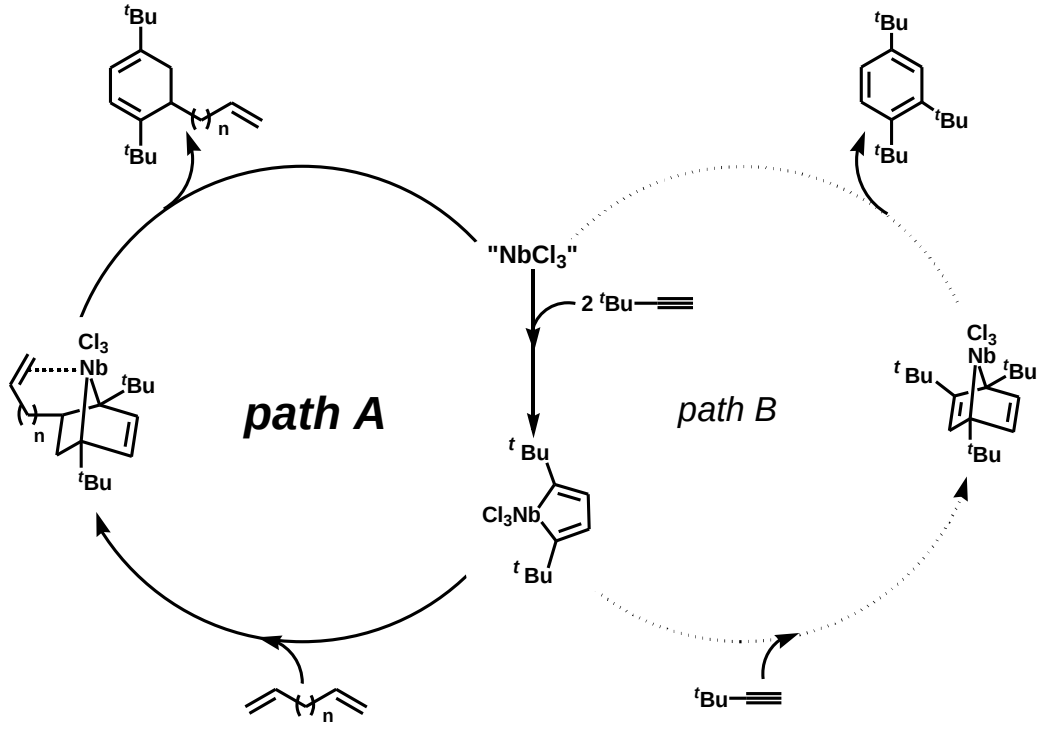
For further exploitation of the synthetic application of the 5-ω-alkenyl-1,4-substituted-1,3-cyclohexadienes, the Pd (II)-catalyzed Wacker oxidation reaction of **3c** was carried out. The reaction of **3c** in the presence of $PdCl_2$ combined with CuCl under O_2 (1 atm)[15] led to the formation of **7**, as ω-acetyl functionalized 1,3-cyclohexadienes in 56% isolated yield (eq 2). Since the substrates having oxo-functionality like ketones and aldehydes are not generally tolerated under the conditions in the low-valent early transition metal catalyst system,[10-12] this two-step synthesis gives an efficient protocol for the 1,3-cyclohexadienes having oxo-functionality in the molecule.



(2)

With regard to the reaction mechanism, the reaction would proceed in a similar manner to the previously reported pathway via the formation of a niobacyclopentadiene (**A**) by the reaction of two alkyne molecules, followed by the reaction with α,ω-dienes to form niobanorbornene species (**B**) as a key intermediate (Scheme 2-4).[14] In the present reaction, however, it was found that the ω-alkenyl moiety on the α,ω-dienes markedly affects the reactivity of the cycloaddition reaction as well as chemo- and regioselectivity. Although all attempts at isolation and spectral observation of the relevant niobium intermediates were unsuccessful, the ω-alkenyl group would coordinate to the niobium metal center as a directing group, which hampered the formation of undesired alkyne

cyclotrimerization products (path A, Scheme 2-4). The directing group effect of the ω-alkenyl moiety presumably enhanced the reactivity of the alkenes, as well as improved selectivity of the resulting 1,3-cyclohexadiene derivatives. However, the effect the chain length of the α,ω-dienes exerted on the regiochemistry of the reaction is not clearly explained at this moment. The detailed elucidation on the reaction mechanism based on the experimental evidence is currently in progress.



Scheme 2-4. A plausible reaction mechanism

2-3. Conclusion

In summary, I have developed a new protocol to the highly chemo- and regioselective reaction for [2 + 2 + 2] cycloaddition of alkynes and alkenes leading to 5-ω-alkenyl-1,4-substituted-1,3-cyclohexadienes in high to excellent yields. In addition, I found that the ω-alkenyl group can be easily converted to the ω-acetyl group.

2-4. Experimental Section

General

GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. The products were characterized by ^{1}H NMR, ^{13}C NMR, HMQC and HMBC.

A Typical Reaction Procedure for the Preparation of 3a (entry 1, Table 1-1)

A mixture of *tert*-butylacetylene (**1a**) (164mg, 2mmol), 1,9-decadiene (**2a**) (552 mg, 4 mmol), $NbCl_3$(DME) (58 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 2 h at 40 ^oC under Ar. The yields of the products were estimated from the peak areas based on the internal standard technique using GC and **3a** was obtained in 97%yield. The product **3a** was isolated by silica gel column chromatography (*n*-hexane as eluent) in 81% yield (489 mg) as a colorless liquid.

The Reaction of 1a with 5 (eq 1)

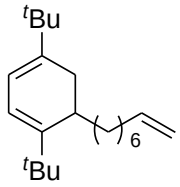
A mixture of tert-butylacetylene (**1a**) (164 mg, 2 mmol), methyl vinylacetate (**5**) (200 mg, 2 mmol), $NbCl_3$(DME) (58 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 2 h at 40 ^oC under Ar. The yields of the products were estimated from the peak areas based on the internal standard technique using GC (68% (**6**) and 8% (**4a**)). The product **6** was isolated as pure form by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2 as eluent) in 55% yield (156 mg) as a colorless liquid.

Preparation of 7 from 3c (eq 2)

A mixture of **3c** (822 mg, 3 mmol), $PdCl_2$ (53 mg, 0.3 mmol), CuCl (297 mg, 3 mmol), and H_2O/DMF (0.3/2.7 mL) was stirred for 24 h at room temperature under O_2 (1 atm). The product **7** was isolated (by silica gel column chromatography with *n*-hexane/ethyl acetate=8:2 as eluent) in 56% yield as pure form (483 mg) as a colorless liquid.

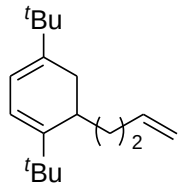
Characterization of the compounds

1,4-Di-*tert*-butyl-5-(oct-7-enyl)cyclohexa-1,3-diene (**3a**), collorless liquid



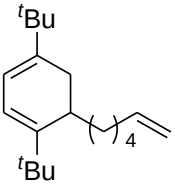
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85-1.02 (m, 2H), 1.05 (s, 9H), 1.09 (s, 9H), 1.28-1.55 (m, 10H), 2.04 (m, 1H), 2.32, (d, 2H), 4.92 (dt, *J*=10.1, 1.7Hz, 1H), 4.98 (dt, *J*=15.4, 1.7Hz, 1H), 5.69 (s, 2H) 5.74 (tt, *J* = 12.4, 5.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.5 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 28.5 (CH_3), 28.7 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.6 (CH_3), 33.2 (CH), 33.8 (CH_2), 35.0 (C), 35.6 (C), 114.1 (CH2), 115.4 (CH), 115.5 (CH), 139.2 (CH), 143.6 (C), 150.2 (C); IR (neat, cm^{-1}) 3069, 1830, 1768, 1648, 1597, 1361, 1103, 921; GC-MS (EI) m/z (rel intensity) 302 (9) $[M]^+$, 190 (1), 175 (6), 119 (4), 79 (1), 57 (100); HRMS (EI) m/z calcd for $C_{22}H_{38}$ $[M]^+$ 302.2974, found 302.2979.

1,4-Di-*tert*-butyl-5-(but-3-enyl)cyclohexa-1,3-diene (**3b**), collorless liquid



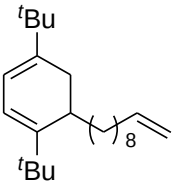
^{1}H-NMR (400 MHz; $CDCl_3$) δ 0.98 (s, 9H), 1.01 (s, 9H), 1.24-1.47 (m, 2H), 1.85-2.10 (m, 2H), 1.98-2.10 (m, 1H), 2.23 (d, *J*=15.1Hz, 2H), 4.85 (dt, *J*=10.1, 1.8Hz, 1H), 4.91 (dt, *J*=15.1, 1.8Hz, 1H), 5.63 (s, 2H), 5.71 (tt, *J* = 11.7, 4.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.3 (CH_2), 28.0 (CH_2), 28.5 (CH_3), 29.6 (CH_3), 31.7 (CH_2), 32.4 (CH), 35.0 (C), 35.6 (C), 114.4 (CH_2), 115.7 (CH), 115.8 (CH), 138.8 (CH), 143.4 (C), 149.8 (C); IR (neat, cm^{-1}) 2963, 2869, 1641, 1479, 1392, 1367, 1264, 1021, 910; GC-MS (EI) m/z (rel intensity) 246 (12) $[M]^+$, 189 (3), 133 (4), 119 (8), 57 (100); HRMS (EI) m/z calcd for $C_{18}H_{30}$ $[M]^+$ 246.2348, found 246.2352.

1,4-Di-*tert*-butyl-5-(hex-5-enyl)cyclohexa-1,3-diene (**3c**), collorless liquid



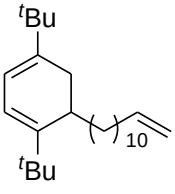
^{1}H-NMR (400 MHz; $CDCl_3$) δ 1.05 (s, 9H), 1.09 (s, 9H), 1.15-1.59 (m, 8H), 2.07 (m, 1H), 2.32 (d, J=14.9 Hz, 2H), 4.92 (dt, J=10.2, 1.7 Hz, 1H), 4.98 (dt, J=15.4, 1.7 Hz, 1H), 5.63 (s, 2H), 5.79 (m, 1H); ^{13}C-NMR(100 MHz, $CDCl_3$) δ 27.0 (CH_2), 28.0 (CH_2), 28.2 (CH_2), 28.5 (CH_3), 29.1 (CH_2), 29.6 (CH_3), 33.2 (CH), 33.8 (CH_2), 35.0 (C), 35.6 (C), 114.2 (CH_2), 115.4 (CH), 115.5 (CH), 139.1 (CH), 143.5 (C), 150.1 (C); IR (neat, cm^{-1}) 2964, 2871, 1736, 1465, 1363, 1062, 885; GC-MS (EI) m/z (rel intensity) 274 (8) $[M]^+$, 175 (6), 83 (1), 79 (1), 57 (100); HRMS(EI)m/z calcd for $C_{20}H_{34}$ $[M]^+$ 274.2661, found 274.2653.

1,4-Di-*tert*-butyl-5-(dec-9-enyl)cyclohexa-1,3-diene (**3d**), collorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.09 (s, 9H), 1.18-1.36 (m, 14H), 1.52 (m, 2H), 2.06 (m, 1H), 2.32 (d, *J*=15.1, 2H), 4.93 (dt, *J*=10.1, 1.4 Hz, 1H), 4.99 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.69 (s, 2H), 5.81 (m, 1H); ^{13}C-NMR(100 MHz, $CDCl_3$) δ 27.5 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 28.4 (CH_3), 28.9 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.5 (CH_3), 29.6 (CH_2), 29.7 (CH_2), 33.2 (CH_3), 33.8 (CH_2), 35.0 (C), 35.6 (C), 114.1 (CH_2), 115.3 (CH), 115.5 (CH), 139.2 (CH), 143.6 (C), 150.3 (C); IR (neat, cm^{-1}) 3056, 1818, 1769, 1642, 1363, 1062, 885; GC-MS (EI) m/z (rel intensity) 330 (8) $[M]^+$, 190 (1), 135 (1), 79 (1), 57 (100); HRMS(EI) m/z calcd for $C_{24}H_{42}$ $[M]^+$ 330.3289, found 330.3294.

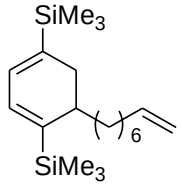
1,4-Di-*tert*-butyl-5-(dodec-11-enyl)cyclohexa-1,3-diene (**3e**), collorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.19-1.49 (m, 18H), 1.18-1.36 (d, *J*=15.2, 2H), 1.32 (s, 9H), 1.94-2.03 (m, 3H), 4.85 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.92 (dt, *J*=15.6, 1.4 Hz, 1H), 5.61 (s, 1H), 5.62 (s, 1H), 5.73 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.6 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 28.5 (CH_3), 28.9 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 29.60 (CH_3), 29.63 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 33.2 (CH),

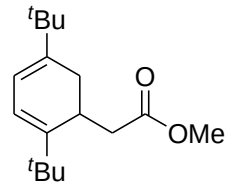
33.8 (CH_2), 35.0 (C), 35.6 (C), 114.0 (CH_2), 115.3 (CH), 115.5 (CH), 139.2 (CH), 143.4 (C), 150.2 (C);GC-MS (EI)m/z (rel intensity) 358 (8) $[M]^+$, 190 (1), 175 (6), 91 (3), 57 (100); HRMS (EI) m/z calcd for $C_{26}H_{46}$ $[M]^+$ 358.3602, found 358.3617.

1,4-Bis(trimethylsilyl)-5-(oct-7-enyl)cyclohexa-1,3-diene (**3f**), collorless liquid



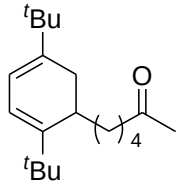
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.03 (s, 9H), 1.11-1.32 (m, 10H), 1.95-2.25 (m, 2H), 1.95-2.27 (d, J = 15.3 Hz, 2H), 2.07 (s, 1H), 4.89 (dt, J = 15.3 Hz, 1H), 5.73 (m, 2H), 6.11 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -2.7 (CH_3), -1.5 (CH_3), 27.3 (CH_2), 27.6 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.4 (CH_2), 32.8 (CH), 33.6 (CH_2), 113.9 (CH_2), 130.8 (CH), 131.5 (CH), 138.2 (CH), 139.0 (C), 145.4 (C); IR (neat, cm^{-1}) 3075, 1640, 1602, 1440, 1247, 1169, 1071, 992; GC-MS (EI) m/z (rel intensity) 334 (3) $[M]^+$, 260 (1), 223 (2), 187 (1), 135 (47), 73 (100), 41 (3);HRMS(EI)m/z calcd for $C_{20}H_{38}Si_2$ $[M]^+$ 334.2512, found 334.2524

Methyl 2-(2,5-di-*tert*-butylcyclohexa-2,4-dienyl)acetate (**6**); collorless liquid



^{1}H-NMR(400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.03 (s, 9H), 2.04 (m, 2H), 2.25-2.50 (m, 2H), 2.73 (m, 1H), 3.53 (s, 3H) 5.65(s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.3 (CH), 29.2 (CH_2), 29.3 (CH_3), 29.5 (CH_3), 33.3 (CH_2), 34.9 (C), 35.6 (C), 51.3 (CH_3), 115.6 (CH), 117.0 (C), 143.8 (C), 147.3 (C), 173.6 (C); IR (neat, cm^{-1}) 2961, 2823, 1738, 1644, 1465, 1362, 1090, 885; GC-MS (EI) m/z (rel intensity) 264 (2) $[M]^+$, 190 (16), 175 (100), 79 (1), 57 (55); HRMS (EI) m/z calcd for $C_{17}H_{28}O_2$ $[M]^+$ 264.2089, found 264.2089

6-(2,5-Di-tert-butylcyclohexa-2,4-dienyl)hexan-2-one (**7**), collorless liquid



^{1}H-NMR(400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.01 (s, 9H), 1.22-1.47 (m, 6H), 1.98 (m, 1H), 2.04 (s, 3H), 2.22 (m, 2H), 2.33 (t, J=7.6 Hz, 2H), 5.62 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_2), 27.0 (CH_2), 27.9 (CH_2), 28.1 (CH_2), 28.4 (CH_3), 29.5 (CH_3), 29.8 (CH_3), 33.0 (CH), 34.9 (C), 35.6 (C), 43.7 (CH_2), 115.5 (CH), 115.6 (CH), 143.5 (C), 149.9 (C), 209.3 (C); IR (neat, cm^{-1}) 3052, 1718, 1462, 1359, 1264, 834; GC-MS (EI) m/z (rel intensity) 290 (9) $[M]^+$, 191 (1), 177 (9), 99(2), 79 (2), 57 (100); HRMS (EI) m/z calcd for $C_{20}H_{34}O$ $[M]^+$ 290.2610 found 290.2613

2-5. Reference

(1) (a) *Dienes in the Diels-Alder Reaction*; Fringuelli, F.; Taticchi, A. Ed. John Wiley: New York. 1990. (b) Aouf, C.; Abed, D, El.; Giorgi, M.; Santelli, M. *Tetrahedron Lett.* **2008**, *49*, 4630. (c) Boyd, D, R.; Sharma, N. D.; Llamas, N. M.; O'Dowd, C, R.; Allen C. C. R. *Org. Biomol. Chem*. **2006**, *4*, 2208. (d) Nguyen, R.-V.; Li, C.-J. *J. Am. Chem. Soc*. **2005**, *127*, 17184. (e) Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem*. **2004**, *69*, 7552. (f) Miller C, A.; Batey, R, A.; *Org. Lett*. **2004**, *6*, 699. (g) Abbott, A, P.; Capper, G.; Davies, D, L.; Rasheed, R, K.; Tambyrajah, V. *Green Chem*., **2002**, *4*, 24. (h) DeCosta, D, P.; Howell, N.; Pincock, A, L.; Pincock, J, A.; Rifai, S. *J. Org. Chem*. **2000**, *65*, 4698. (i) Thorarensen, A.; Palmgren, A.; Itami, K.; Bäckvall, J, -E. *Tetrahedron Lett*. **1997**, *38*, 8541. (j) Hartsough, D.; Schuster, G, B, *J. Org. Chem*. **1989**, *54*, 3 and references therein.

(2) For example, (a) Heiser, D, E.; Okuda, J.; Gambarotta, S.; Müelhaupt, R. Macromol. *Chem. Phys*. **2005**, *206*, 195. (b) Natori, I. *Macromolecules*. **1997**, *30*, 3696 and references therein.

(3) (a) Lautens, M.; Ma, S.; Belter, R, K.; Chiu, P.; Leschziner, A. *J. Org. Chem*. **1992**, *57*, 4065. (b) Berchtold, G, A.; Ciabattoni, J.; Tunick, A, A. *J. Org. Chem*. **1965**, *30*, 3679. (c) Dyachenko, V, D.; Dyachenko, A, D.; Chernega, A, N. Russ. *J. Org. Chem*. **2004**, *40*, 397. (d) Weisz, A.; Mandelbaum, A. *J. Org. Chem*. **1984**, *49*, 2648. (e) Lasnier, G.; Wiemann, J. *C. R. Seances Acad. Sci. Ser. C.* **1969**, *268*, 1891 (f) Zupancic, B, G.; Wucherpfennig, W. *Chem. Ber*. **1967**, *100*, 1764.

(4) (a) Peppers, B, P.; Kulkarni, A, A.; Diver, S, T. *Org. Lett.* **2006**, *8*, 2539. (b) Middleton, M, D.; Diver, S, T. *Tetrahedron Lett*. **2005**, *46*, 4039.

(5) Brandänge, S.; Leijonmarck, H. *Chem. Commun*. **2004**, 292.

(6) (a) Vollhardt, K, P, C. *Angew. Chem., Int. Ed*. **1984**, *23*, 539. (b) Schore, N, E. *Chem. Rev*. **1988**, *88*, 1081. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev*. **1996**, *96*, 49. (d) Negishi, E.; Copéret, C.; Ma, S.; Liou, S,-Y.; Liu, F. *Chem. Rev*. **1996**, *96*, 365. (e) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R, J, *Chem. Rev.* **1996**, *96*, 635. (f) Saito, S.; Yamamoto, Y. *Chem. Rev*. **2000**, *100*, 2901. (g) Cadierno, V.; Garcia-Garrido, S, E.; Gimeno, J. *J. Am. Chem. Soc*. **2006**, *128*, 15094 and references therein.

(7) (a) Oshiki, T.; Nomoto, H.; Tanaka, K.;Takai, K. *Bull. Chem. Soc. Jpn*. **2004,** *77*, 1009. (b) Du, J, A, K.; Viljoen, J, S.; Du Toit, C, J. *J. Mol. Cat*. **1991**, *64*, 269.

(8) (a) Balaich, G, J.; Rothwell, I, P. *J. Am. Chem. Soc*. **1993**, *115*, 1581. (b) Johnson, E, S.; Balaich, G, J.; Rothwell, I, P. *J. Am. Chem. Soc*. **1997**, *119*, 7685.

(9) Hilt, G.; Paul, A.; Harms, K. *J. Org. Chem*. **2008**, *73*, 5187.

(10) (a) Obora, Y.; Kimura, M.; Tokunaga, M.;Tsuji, Y. *Chem. Commun*. **2005**, 901. (b) Y. Obora, M. Kimura, T. Ohtake, M. Tokunaga, Y. Tsuji, *Organometallics*, **2006**, *25*, 2097.

(11) (a) E. J. Roskamp and S. F. Pedersen, *J. Am. Chem. Soc*, **1987**, *109*, 6551. (b) Hartung, J, B.; Pedersen, S, F. *J. Am. Chem. Soc*. **1989**, *111*, 5468. (c) Roskamp, E, J.; Dragovich, P, S.; Hartung, J, B.; Pedersen, S, F. *J. Org. Chem*. **1989**, *54*, 4736. (d) Hartung, J, B.; Pedersen, S, F. *Organometallics*.

1990, *9*, 1414.

(12) (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utinoto, K. *J. Org. Chem*. **1992**, *57*, 1973. (b) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett*. 1990, *31*, 365. (c) Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, T. *Tetrahedron Lett*. 1990, *31*, 369. (d) Fürstner, A.; Hupperts, A.; Ptock A.; Janssen, E. *J. Org. Chem.* 1994, *59*, 5215. (e) Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron*. **1992**, *48*, 3867.

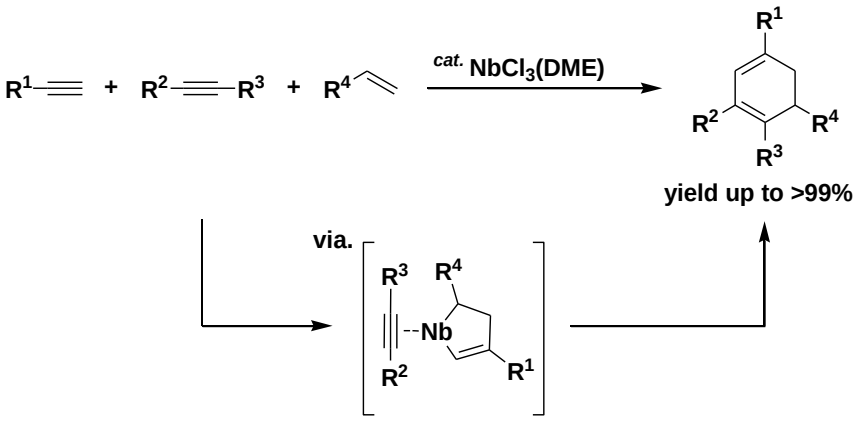
(13) (a) Fuchibe, K.; Mitomi, K.; Suzuki, R.; Akiyama, T. *Chem. Asian. J*. **2008**, *3*, 261. (b) Fuchibe, K.; Oshima, Y.; Mitomi, K.; Akiyama, T. *Org. Lett*. **2007**, *9*, 1497. (c) Fuchibe, K.; Mitomi, K.; Akiyama, T. *Chem. Lett.* **2007**, *36*, 24. (d) Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc*. **2006**, *128*, 1434.

(14) Obora, Y.; Takeshita, K.; Ishii, Y. *Org. Biomol. Chem.* **2009**, *7*, 428.

(15) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth*. **1984**, *62*, 9.

Chapter 3

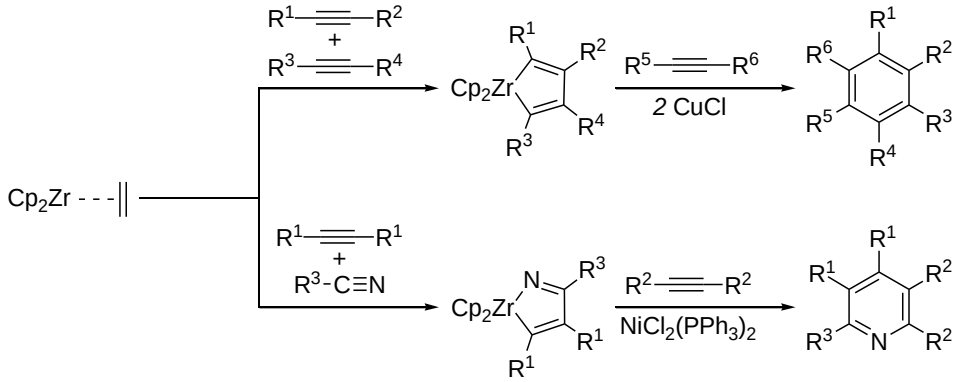
$NbCl_3$-catalyzed Three-component [2+2+2] Cycloaddition Reaction of Terminal Alkynes, Internal Alkynes, and Alkenes to 1,3,4,5-Tetrasubstituted 1,3-Cyclohexadienes



3-1. Introduction

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition of unsaturated compounds has been extensively studied for the formation of various aromatic and unsaturated cyclic compounds.[1] In general, this protocol is selectively accomplished by intramolecular reactions using diynes and dienes as substrates. Chemo- and stereocontrolled intermolecular [2 + 2 + 2] cycloadditions, in particular from three different substrates, are, therefore, highly desirable and a challenging target. To date, several examples of chemoselective transition-metal-catalyzed or –mediated alkyne cyclotrimerizations from three different alkynes, leading to multisubstituted aromatic compounds, have been reported (Scheme 3-1).[2,3]

Takahashi (ref. 2)



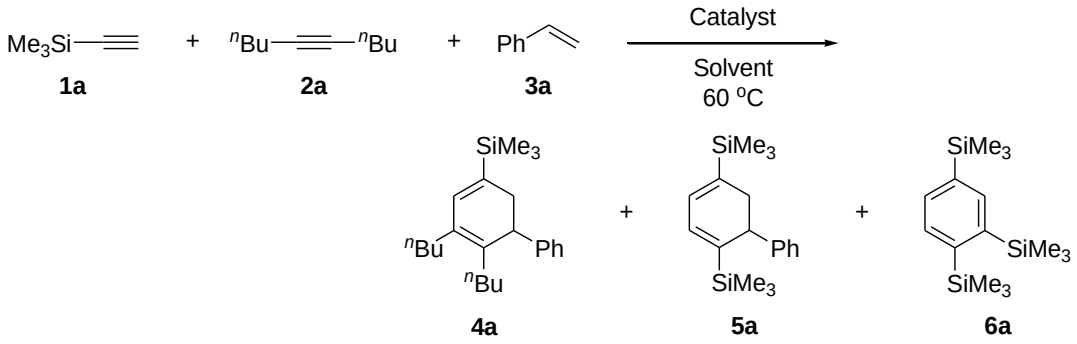
Scheme 3-1. Chemoselective intermolecular reaction of internal alkynes and nitriles by zirconacyclopentenes

1,3-Cyclohexadienes are an important class of compounds and are widely used in organic and polymer chemistry.[4,5] Among the various synthetic methods for the synthesis of 1,3-cyclohexadienes reported so far,[6] transition-metal-catalyzed [2 + 2 + 2] cycloaddition from easily accessible unsaturated compounds, such as simple alkynes and alkenes, is the most favorable. However, in contrast to the case of cycloaddition by alkyne trimerization, only a limited amount of work on the synthesis of 1,3-cyclohexadienes by intermolecular cycloaddition of alkynes and alkenes has been reported because of the difficulty in controlling the chemo- and regioselectivity.[7,8] $NbCl_3$(DME) is a thermally stable low-valent early transition-metal complex,which has been used as a reagent in the reactions of alkynes with several electrophiles.[9-12] My group recently reported that $NbCl_3$(DME) serves as an efficient catalyst for intermolecular cycloaddition of two molecules of terminal alkynes and one alkene or α,ω-diene molecule to afford 1,4,5-trisubstituted-1,3-cyclohexadienes.[13]

3-2. Result and Discussion

The reaction of trimethylsilylacetylene (**1a**), 5-decyne (**2a**), and styrene (**3a**) was chosen as a model reaction and was carried out under various conditions (Table 3-1).

Table 3-1 $NbCl_3$(DME)-Catalyzed [2 + 2 + 2]-Cycloaddition of **1a**, **2a**, and **3a**[a]



			Yield (%)		
Entry	Catalyst	Solvent	**4a**[b]	**5a**[c]	**6a**[d]
1	$NbCl_3$(DME)	1,2-Dichloroethane	99 (97)	trace	n.d.[e]
2[f]	$NbCl_3$(DME)	1,2-Dichloroethane	62	5	trace
3[g]	$NbCl_3$(DME)	1,2-Dichloroethane	56	trace	trace
4[h]	$NbCl_3$(DME)	1,2-Dichloroethane	72	9	12
5	$NbCl_3$(DME)	1,4-Dichlorobutane	82	5	8
6	$NbCl_3$(DME)	Toluene	77	trace	10
7[i]	$NbCl_3$(DME)	Dioxane	58	trace	trace
8	$NbCl_3$(DME)	THF	3	n.d.[e]	n.d.[e]
9	$NbCl_3$(DME)	DME	n.d.[e]	n.d.[e]	n.d.[e]
10	$TaCl_3$(DME)	1,2-Dichloroethane	n.d.[e]	n.d.[e]	n.d.[e]
11	$NbCl_5$	1,2-Dichloroethane	trace	13	6
12	Cp_2NbCl_2	1,2-Dichloroethane	n.d.[e]	n.d.[e]	n.d.[e]

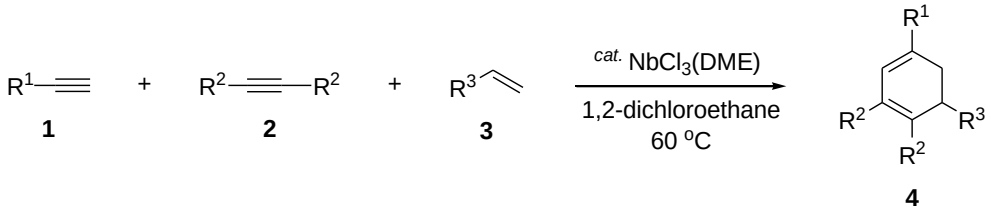
(a) Reaction conditions: **1a** (2 mmol), **2a** (1 mmol), **3a** (4 mmol), and catalyst (0.2 mmol) in solvent (1 mL) at 60 °C for 16 h. (b) Determined by GC based on **2a** used. The number in parentheses shows isolated yield. (c) Determined by GC based on **1a** used. Compound **5a** was exclusively obtained as 1,4,5-adduct. (d) Determined by GC based on 1a used. Compound **6a** was exclusively obtained as 1,4,5-adduct. (e) Not detected by GC. (f) Reaction was performed using $NbCl_3$(DME) (0.2 mmol), **1a** (1 mmol), **2a** (1 mmol), and **3a** (1 mmol). (g) Reaction was performed using $NbCl_3$(DME) (0.2 mmol), **1a** (2 mmol), **2a** (2 mmol), and **3a** (2 mmol). (h) Reaction was performed using $NbCl_3$(DME) (0.2 mmol), **1a** (4 mmol), **2a** (2 mmol) and **3a** (2 mmol). (i) The reaction was performed at 80 °C.

For exanmple, **1a** (2 mmol) was allowed to react with **2a** (1 mmol) and **3a** (4 mmol) under the influence of $NbCl_3$(DME) (0.2 mmol) in 1,2-dichloroethane (1 mL) at 60 ^oC for 16 h. 1-Trimethylsilyl-3,4-*n*-dibutyl-5-phenyl-1,3-cyclohexadiene (**4a**) was obtained in quantitative yield with excellent chemo- and regioselectivity (Table 3-1, entry 1). It is noteworthy that the reaction led exclusively to intermolecular three-component cross-cycloaddition products from three different substrates, in preference to the cyclotrimerization of terminal alkynes (leading to **6a**)[11] and cross-cycloaddition reactions of terminal alkynes with alkenes (leading to **5a**).[7,8,13]

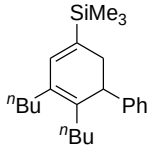
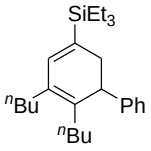
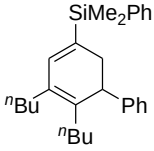
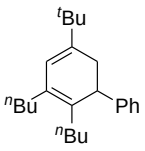
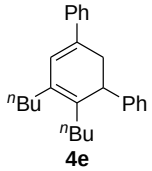
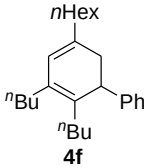
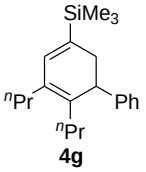
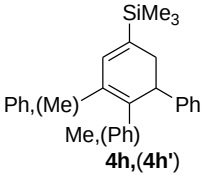
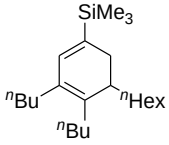
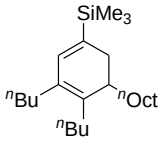
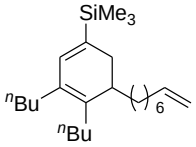
The substrates ratio markedly influenced the selectivity and yield of the desired product **4a**. On screening the reaction, I found that the optimized reaction ratio of **1a**:**2a**:**3a** is 2:1:4 (entry 1). Nevertheless, even if **1a**, **2a**, and **3a** were allowed to react in a stoichiometric ratio (**1a**:**2a**:**3a**=1:1:1), the yield of the desired 1,3-cyclohexadiene was still acceptable (62%) (entry 2). In addition, chemoselective (entry 3) and high yield formation (entry 4) of **4a** was achieved by tuning the ratio of the substrates (**1a**:**2a**:**3a**) with smaller amounts (10 mol %) of $NbCl_3$ catalyst. With regard to the solvent, **4a** was obtained in high yields when halogenated solvents such as 1,2-dichloroethane and 1,4-dichlorobutane were used (entries 1-5). However, toluene and dioxane were tolerated as solvents (entries 6 and 7). The catalyst precursor significantly influenced the reaction activity: the low-valent Nb(III) complex, $NbCl_3$(DME), is highly efficient (entry 1). When the Ta(III) analogue, $TaCl_3$(DME), was used as a catalyst, all the substrates were evidently converted in the course of the reaction, but only an intractable mixture of oligomeric products was obtained under these conditions (entry 10). Other Nb(IV), Nb(V), and V(III) complexes, such as $NbCl_5$ and Cp_2NbCl_2, were totally ineffective as catalysts for the cycloaddition reactions (entries 11 and 12).

Under the optimized conditions shown in Table 3-1, entry 1, the reactions of various terminal alkynes (**1**), internal alkynes (**2**), and 1-alkenes (**3**) were investigated (Table 3-1). The chemo- and regioselectivities of the adducts were significantly influenced by the bulkiness of the substituents on the terminal alkynes (**1**) used in the reaction. Thus, reactions using trialkylsilylacetylenes, such as trimethylsilylacetylene (**1a**), triethylsilylacetylene (**1b**), and dimethylphenylsilylacetylene (**1c**), provide the corresponding 1,3,4,5-tetrasubstituted-1,3-cyclohexadiene derivatives (**4a-c**) in excellent yield, as the sole product, and with excellent chemo- and regioselectivity (entries 1-3). *tert*-Butylacetylene was also a good substrate for the formation of three-component cycloaddition products in high yield, along with the formation of **5d** (12%) and **6d** (4%) as by-product. The regioselectivity for the 1,3,4,5-adduct (**4d**) was good but not completely selective (71%) (entry 4). The use of less bulky terminal alkynes such as phenylacetylene and 1-octyne did not give the desired three-component coupling products, but alkyne cyclotrimerization products were obtained in considerable yields (entries 5 and 6).

Table 3-2. $NbCl_3$(DME)-Catalyzed Reactions of Various Terminal Alkynes **1**, Internal Alkynes **2**, and Alkenes **3** Leading to Tetrasubstituted 1,3-Cyclohexadienes **4**[a]



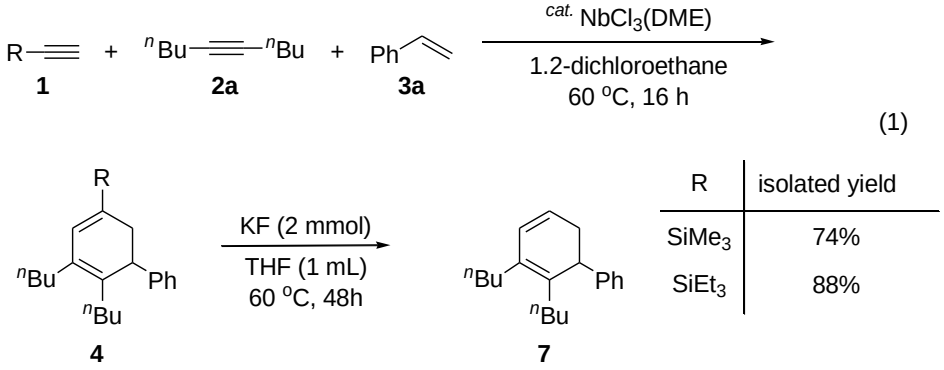
1 **2** **3** **4**

	Yield (%) of **4**[b]						
1	 **4a**	2	 **4b**	3	 **4c**	4	 **4d**
	97[c]		85[c]		83[c]		89[d,e,f], 71[g]
5	 **4e**	6	 **4f**	7	 **4g**	8	 **4h,(4h')**
	56[d,f,hc], 40[g]		25[d,i], 79[g]		99[c]		91[c] (**4h**:(**4h'**)=1:1)
9	 **4i**	10	 **4j**	11	 **4k**		
	92[c,j]		72[c,k]		97[c,l]		

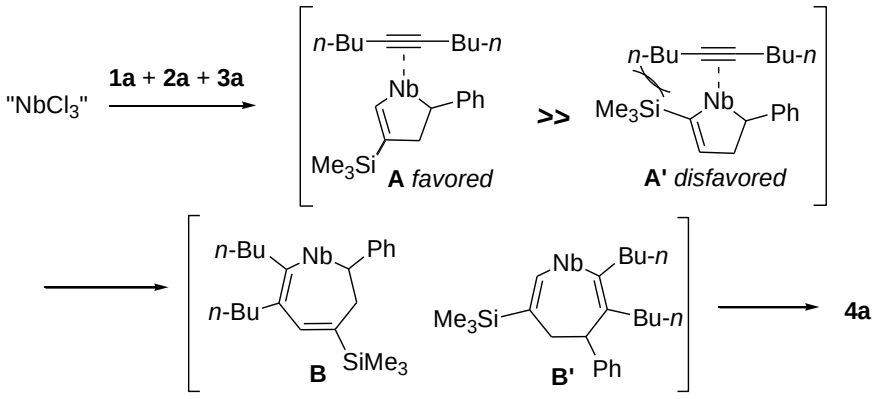
(a) Reaction conditions: **1** (2 mmol), **2** (1 mmol), **3** (4 mmol), and $NbCl_3$(DME) (0.2 mmol) in 1,2-dichloroethane (1 mL) at 60 °C, 16 h. (b) Isolated yields unless otherwise noted. (c) Compound **4** was obtained exclusively as the 1,3,4,5-adducts. (d) Regioisomers (entries 4-6) of **4** were identified by GC and GC-MS, and the yields were determined by GC. The structures of the major regioisomers (1,3,4,5-addducts) are shown in the table. The products were isolated as a mixture of **4**-**6** due to difficulty in completely separating them. (e) The major regioisomer (1,3,4,5-adduct) of **4d** was isolated in 63% yield. (f) In addition to the product **4d**, **5d** (12%) and **6d** (4%) were formed. (g) Regioselectivity (%) of the 1,3,4,5-adducts in the total regioisomers of **4**. The regiochemistry of the other isomers was not determined. (h) In addition to the product **4e**, **6e** (18%) was formed. (i) In addition to the product **4f**, **5f** (8%) and 6f (59%) were formed. (j) In addition to the product **4i**, **5i** (8%) and **6i** (12%) were formed. (k) In addition to the product **4j**, **6i** (13%) was formed. (l) In addition to the product **4k**, **5k** (8%) and **6k** (10%) were formed.

Similarly, 4-octyne and 1-phenyl-1-propyne were allowed to react with **1a** and **3a**, affording the corresponding 1,3,4,5-tetrasubstituted-1,3-cyclohexadiene derivatives (**4g** and **4h**) in excellent yields with excellent chemo- and regioselectivity (entries 7 and 8). In addition, the reaction tolerated the use of unactivated simple alkenes, such as 1-octene and 1-decene, giving the desired three-component cycloaddition adducts in high yields with high regioselectivity (entries 9 and 10). It is noteworthy that the reactions of α,ω-dienes with **1a** and **2a** took place exclusively at one side, affording 5-ω-alkenyl-1,3,4,5-tetrasubstituted-1,3-cyclohexadienes in high yield with high regioselectivity (entry 11).

In addition, we found that 3,4,5-trisubstituted 1,3-cyclohexadienes have been synthesized by desilylation[14] from the 1,3,4,5-tetrasubstituted 1,3-cyclohexadienes obtained in this study. Thus, addition of KF (2 mmol) and THF (1 mL) to a reaction mixture prepared under the reaction conditions shown in Table 3-1, entry 1, gave 3,4-di-*n*-butyl-5-phenyl-1,3-cyclohexadiene (**7**) in good isolated yields (74% with $R^1 = SiMe_3$ and 88% with $R^1 = SiEt_3$; eq 1). This one-pot and high-yield synthesis provides an efficient and versatile protocol for the synthesis of various 3,4,5-trisubstituted 1,3-cyclohexadienes.



Although it is not possible to confirma detailed reaction mechanism at this stage, the present three-componentcycloaddition of **1a**, **2a**, and **3a** is thought to proceed by the following pathway (Scheme 3-2). The reaction initiates oxidative cyclometalation of the terminal alkyne (**1a**) and terminal alkene (**3a**); coordination of the internal alkyne (**2a**) to the Nb center gives a niobacyclopentene intermediate (**A**). Bulky substituents such as a trimethylsilyl group would lead to preferential formation of **A** rather than the sterically congested form **A'**.[15] Subsequently, divergent migratory insertion of the coordinated internal alkyne **2a** into theNb-vinyl bond or the Nb-alkyl bond occurs to form **B** and **B**', respectively.[15,16] Insertion into the less-hindered Nb-vinyl bonds would be favored, affording the niobacyclic intermediate **B**.[17] **B** then exclusively produces the three-component coupling product 1,3,4,5-tetrasubstituted 1,3-cyclohexadiene **4a**.



Scheme 3-2. A plausible reaction mechanism

3-3. Conclusion

In conclusion, I have found a new highly active catalytic system for chemo- and regioselective [2 + 2 + 2] intermolecular cycloaddition reactions of terminal alkynes, internal alkynes, and alkenes to 1,3,4,5-tetrasubstituted-1,3-cyclohexadiene derivatives.

3-4. Experimental Section

General

GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. The products were characterized by ^{1}H NMR, ^{13}C NMR, HMQC and HMBC.

A typical reaction procedure for the preparation of 3a (entry 1, Table 1):

A mixture of trimethylsilylacetylene (**1a**) (196 mg, 2 mmol), 5-decyne (**2a**) (138 mg, 1 mmol), styrene (**3a**) (417 mg, 4 mmol), $NbCl_3$(DME) (58 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 16 h at 60 ˚C under Ar. The yields of the products were estimated from the peak areas based on the internal standard technique using GC and **4a** was obtained in quantitative yield. The products **3a** was isolated by silica gel column chromatography (*n*-hexane as eluent) in 97% yield (330 mg) as colorless liquid.

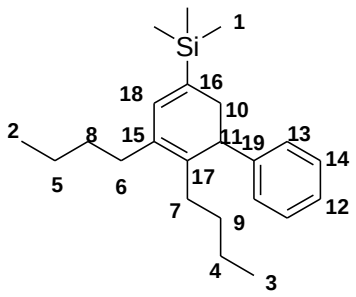
Preperation of 7 from 1a,2a and 3a

A mixture of trimethylsilylacetylene (**1a**) (196 mg, 2 mmol), 5-decyne (**2a**) (138 mg, 1 mmol), styrene (**3a**) (417 mg, 4 mmol), $NbCl_3$(DME) (58 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 16 h at 60 ˚C under Ar. Subsequently, KF (116 mg, 2 mmol) and THF (1 mL) were added to the reaction mixtures and reacted it for 48 h at 60 ˚C under Ar. The products **7** was isolated

by silica gel column chromatography (*n*-hexane as eluent) in 74% yield (203 mg) as colorless liquid.

Charactarization of the compounds

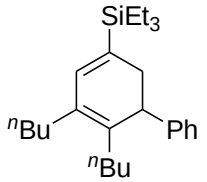
(3,4-Dibutyl-5-phenylcyclohexa-1,3-dienyl)trimethylsilane (**4a**); colorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.96-1.10 (m, 6H), 1.37-1.62 (m, 4H), 2.24-2.49 (m, 8H), 2.50-2.70 (d, 2H), 3.42, (d, 1H), 6.25 (s, 1H), 7.26-7.34 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 0.0 ($Si(CH_3)_3$), 16.8 (CH_3), 16.9 (CH_3), 25.68 (CH_2), 25.71 (CH_2), 33.8 (CH_2), 34.1 (CH_2), 34.71 (CH_2), 34.73 (CH_2), 37.4 (CH_2), 44.6 (CH), 128.7 (CH), 130.6 (CH), 130.7 (CH), 134.2 (C), 136.1 (C), 138.3 (C), 139.1 (CH) 146.1 (C); IR (neat, cm^{-1}) 3061, 2815, 1934, 1741, 1601, 1031, 980; GC-MS (EI) *m/z* (relative intensity) 340 (12) [M^+], 283 (5), 267 (6), 210 (1), 75 (4), 73 (100), 57(6), 28 (1); HRMS (EI) *m/z* calcd for $C_{23}H_{36}Si$ [M]$^+$ 340.2586, found 340.2580.

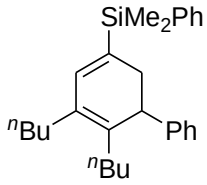
	C	Class	H	HMQC	HMBC	Correlated H
1	0.00	CH_3	0.00	0.25	0.00	**1**
2	16.79	CH_3	0.96-1.00	1.14		
3	16.89	CH_3	1.06-1.10	1.24		
4	25.68	CH_2	1.37-1.62	1.54	1.06	**2**
5	25.71	CH_2	1.37-1.62	1.66	1.06	**3**
6	33.82	CH_2	2.24	2.29	1.56,6.14	**5,18**
7	34.06	CH_2	2.24	2.29	1.48,3.36	**4,11**
8	34.71	CH_2	2.35-2.49	2.47		
9	34.73	CH_2	2.35-2.49	2.47		
10	37.35	CH_2	2.50,2.70	2.50,2.72	3.34,6.14	**11,18**
11	44.57	CH	3.42	3.39	2.39,2.42,2.65,7.15	**7,10,13**
12	128.67	CH	7.26-7.34	6.87	7.15	**13**
13	130.57	CH	7.26-7.34	6.94	3.37,7.19	**11,12,13**
14	130.67	CH	7.26-7.34	6.94	7.19	**14**
15	134.22	C	×	×	2.25,2.34,3.37	**8,11**
16	136.08	C	×	×	0.00,3.39	**1,11**
17	138.29	C	×	×	2.44,2.58,6.14	**10,18**
18	139.09	CH	6.25	5.92	2.22,2.43,2.64	**6,10**
19	146.13	C	×	×	2.46,2.65,3.37,7.20	**10,11,14**

(3,4-Dibutyl-5-phenylcyclohexa-1,3-dienyl)triethylsilane (**4b**)**:** colorless liquid



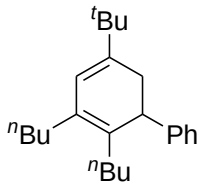
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85-0.89 (t, 9H), 0.99-1.64 (m, 20H), 2.31-2.53 (m, 4H), 2.68 (d, 1H), 3.45 (d, 2H), 6.25 (s, 1H), 7.27-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.3 (CH_2), 7.1 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 22.9 (CH_2), 23.0 (CH_2), 31.0 (CH_2), 31.4 (CH_2), 31.98 (CH_2), 32.01 (CH), 35.4 (CH_2), 41.7 (CH_2), 125.9 (CH), 127.8 (CH), 128.1 (CH), 130.5 (C), 131.7 (C), 135.2 (C), 138.1 (C), 143.2 (C); IR (neat, cm^{-1}) 3061, 2955, 1937, 1798, 1569, 1073, 1008; GC-MS (EI) *m/z* (relative intensity) 382 (2) [M^+], 325 (3), 226 (10), 155 (2), 115 (100), 57(6); HRMS (EI) *m/z* calcd for $C_{26}H_{42}Si$ [M]$^+$ 382.3056, found 382.5055.

(3,4-Dibutyl-5-phenylcyclohexa-1,3-dienyl)dimethyl(phenyl)silane (**4c**); colorless liquid



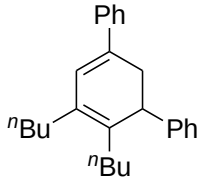
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.00 (s, 3H), 0.64-0.68 (t, *J*=6.6 Hz, 3H), 0.75-0.78 (t, *J*=7.1 Hz, 3H), 1.05-1.49 (m, 12H), 2.18-2.37 (m, 2H), 3.12-3.14 (d, 1H), 6.02 (s, 1H), 6.92-7.06 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -3.83 (CH_3), -3.70 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 22.9 (CH_2), 23.0 (CH_2), 31.0 (CH_2), 31.4 (CH_2), 31.97 (CH_2), 31.98 (CH_2), 35.0 (CH_2), 41.7 (CH), 126.0 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 130.9 (C), 131.8 (C), 133.9 (CH),135.8 (C), 138.4 (CH), 138.7 (C), 143.0 (C); IR (neat, cm^{-1}) 3066, 2927, 1950, 1571, 1492, 1246, 981, 808; GC-MS (EI) *m/z* (relative intensity) 402 (8) [M^+], 385 (6), 343 (11), 266 (9), 167 (5), 135(100), 57(5); HRMS (EI) *m/z* calcd for $C_{28}H_{38}Si$ [M]$^+$ 402.2743, found 402.2770.

1-(5-*tert*-Butyl-2,3-dibutylcyclohexa-2,4-dienyl)benzene (**4d**)**:** colorless liquid



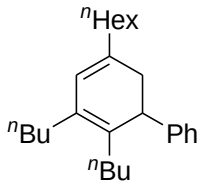
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.74 (s, 9H), 0.87-1.08 (m, 6H), 1.23-1.40 (m, 4H), 1.60 (m, 4H), 2.43-2.51 (m, 4H), 2.54, (d, 2H), 3.29 (d, 1H), 5.58 (s, 1H), 7.08-7.15 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 2.3 (CH_2), 7.1 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 22.9 (CH_2), 23.0 (CH_2), 31.0 (CH_2), 31.4 (CH_2), 31.98 (CH_2), 32.01 (CH), 35.4 (CH_2), 41.7 (CH_2), 125.9 (CH), 127.8 (CH), 128.1 (CH), 130.5 (C), 131.7 (C), 135.2 (C), 138.1 (C), 143.2 (C); IR (neat, cm^{-1}) 3081, 2966, 1938, 1859, 1802, 1656, 1600, 1377, 1031, 852; GC-MS (EI) *m/z* (relative intensity) 324 (19) [M^+], 267 (15), 211 (30), 155 (19), 79 (2), 77 (2)57 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{36}$ [M]$^+$ 324.2817, found 324.2802.;Other isomers : GC-MS (EI) *m/z* (relative intensity) 324 (6) [M^+], 267 (21), 211 (22), 155 (14), 91 (10), 77 (1)57 (100), 324 (32) [M^+], 267 (47), 211 (20), 155 (19), 79 (3), 77 (4)57 (100), 324 (21) [M^+], 267 (16), 211 (26), 155 (17), 79 (2), 77 (2)57 (100).; HRMS (EI) *m/z* calcd for $C_{24}H_{36}$ [M]$^+$ 324.2817, found 324.2848, 324.2807, 324.2850

1-(2,3-Dibutyl-5-phenylcyclohexa-2,4-dienyl)benzene (**4e**)**:** colorless liquid



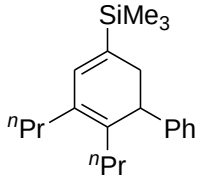
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.61-2.91 (m, 20H), 3.74 (d, 1H), 6.50 (s, 1H), 6.98-7.08 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 14.1 (CH_3), 22.4 (CH_2), 22.7 (CH_2), 30.0 (CH_2), 31.1 (CH_2), 31.8 (CH_2), 32.2 (CH_2), 38.0 (CH_2), 41.7 (CH), 125.0 (CH), 126.2 (CH), 126.5 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.3 (CH), 130.2 (C), 134.9 (C), 140.7 (C), 142.5 (C); IR (neat, cm^{-1}) 3058, 2857, 1943, 1881, 1793, 1644, 1492, 1377, 1377, 852; GC-MS (EI) *m/z* (relative intensity) 344 (100) [M^+], 287 (51), 211 (8), 192 (1), 155 (14), 79 (2), 77 (4), 57 (2), 29(10); HRMS (EI) *m/z* calcd for $C_{26}H_{32}$ [M]$^+$ 344.2504, found 324.2505, GC-MS (EI) *m/z* (relative intensity) 344 (63) [M^+], 300 (100), 211 (13), 192 (6), 155 (24), 149 (55), 79 (4), 57 (13), 29(15); HRMS (EI) *m/z* calcd for $C_{26}H_{32}$ [M]$^+$ 344.2504, found 324.2498.; Other isomers: GC-MS (EI) *m/z* (relative intensity) 344 (100) [M^+], 301 (32), 211 (8), 192 (3), 155 (14), 91 (56), 79 (2), 57 (24), 29(12);HRMS (EI) *m/z* calcd for $C_{26}H_{32}$ [M]$^+$ 344.2504, found 324.2505.

1-(2,3-Dibutyl-5-hexylcyclohexa-2,4-dienyl)benzene (**4f**)**:** colorless liquid



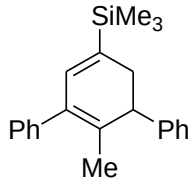
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84-0.99 (m, 9H), 1.15-2.58 (m, 24H), 3.35 (s, 1H), 7.19-7.24 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.1 ($3CH_3$), 22.7-37.7 ($12CH_2$), 43.0 (CH), 127.8-128.1 (3CH), 129.9 (CH), 134.7 (C), 139.7 (C), 143.6 (C), 144.4 (C); IR (neat, cm^{-1}) 2935, 1658, 1602, 1460, 1377, 1103, 823; C-MS (EI) *m/z* (relative intensity) 352 (2) [M^+], 295 (4), 239 (5), 155 (5), 117 (31), 91 (100), 85 (2), 79 (2), 77 (6); HRMS (EI) *m/z* calcd for $C_{26}H_{40}$ [M]$^+$ 352.3130, found 352.3132.; Other isomers.: GC-MS (EI) *m/z* (relative intensity) 352 (48) [M^+], 295 (100), 239 (24), 155 (55), 117 (8), 91 (66), 85 (45), 79 (8), 77 (4) ;HRMS (EI) *m/z* calcd for $C_{26}H_{40}$ [M]$^+$ 352.3130, found 352.356.

Trimethyl(5-phenyl-3,4-dipropylcyclohexa-1,3-dienyl)silane (**4g**)**:** colorless liquid



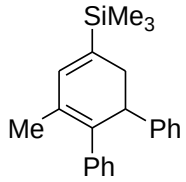
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.99-1.02 (t, 3H), 1.09-1.12 (t, 3H), 1.46-1.67 (m, 4H), 2.23-2.50 (m, 4H), 2.67-2.74 (d, 2H), 3.43 (d, 1H), 6.25 (s, 1H), 7.26-7.35 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 0.1 ($Si(CH_3)_3$), 17.08 (CH_3), 17.12 (CH_3), 25.5 (CH_2), 25.7 (CH_2), 36.1 (CH_2), 36.5 (CH_2), 37.7 (CH_2), 44.6 (CH), 128.7 (CH), 130.6 (CH), 130.7 (CH), 134.3 (C), 136.1 (C), 138.3 (C), 139.1 (CH) 146.2 (C); IR (neat, cm^{-1}) 3061, 2815, 1937, 1794, 1662, 1600, 982; GC-MS (EI) *m/z* (relative intensity) 312 (13) [M^+], 269 (5), 239 (6), 162 (6), 77 (1), 73 (100), 43(6); HRMS (EI) *m/z* calcd for $C_{21}H_{32}Si$ [M]$^+$ 312.2273, found 312.2277.

Trimethyl(4-methyl-3,5-diphenylcyclohexa-1,3-dienyl)silane (**4h**)**:** colorless liquid



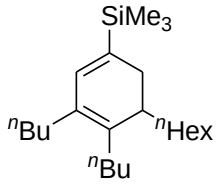
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 1.74 (s, 3H), 2.49-2.58 (d, 2H), 3.44-3.47 (d, 1H), 6.31 (s, 1H), 7.16-7.45 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -2.9 ($Si(CH_3)_3$), 19.08 (CH_3), 35.0 (CH_2), 44.8 (CH), 125.9-128.7 (6CH), 133.5 (C), 134.0 (C), 135.8 (C), 135.9 (C), 141.7 (C), 142.8 (C); IR (neat, cm^{-1}) 3080, 2953, 2811, 1940, 1867, 1798, 1734, 1572, 1491, 1450, 1247, 835; GC-MS (EI) *m/z* (relative intensity) 318 (25) [M^+], 303 (4), 245 (25), 241 (2), 165 (5), 77 (2), 73(100); HRMS (EI) *m/z* calcd for $C_{22}H_{26}Si$ [M]$^+$ 318.1804, found 318.1796.

Trimethyl(3-methyl-4,5-diphenylcyclohexa-1,3-dienyl)silane (**4h'**)**:** colorless liquid



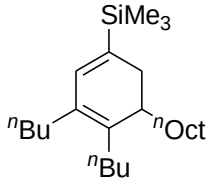
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 1.94 (s, 3H), 2.78-2.92 (d, 2H), 3.44-3.47 (d, 1H), 6.38 (s, 1H), 7.16-7.45 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.7 ($Si(CH_3)_3$), 19.6 (CH_3),34.0 (CH_2), 44.2 (CH), 125.9-128.7 (6CH), 133.6 (C), 134.8 (C), 135.8 (C), 137.3 (CH), 142.0 (C), 143.2 (C); IR (neat, cm^{-1}) 3080, 2953, 2811, 1940, 1867, 1798, 1734, 1572, 1491, 1450, 1247, 835; GC-MS (EI) *m/z* (relative intensity) 318 (19) [M^+], 303 (9), 245 (16), 241 (1), 165 (4), 77 (2), 73(100); HRMS (EI) *m/z* calcd for $C_{22}H_{26}Si$ [M]$^+$ 318.1804, found 318.1796.

(3,4-Dibutyl-5-hexylcyclohexa-1,3-dienyl)trimethylsilane (**4i**)**:** colorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9H), 0.79-0.87 (m, 9H), 1.02-1.42-1 (m, 18H), 1.64-2.30 (m, 7H), 5.95 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -1.4 ($Si(CH_3)_3$), 15.06 (CH_3), 15.08 (CH_3), 15.1 (CH_3), 23.7 (CH_2), 24.1 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 30.5 (CH_2), 31.6 (CH_2), 31.7 (CH_2), 32.3 (CH_2), 32.9 (CH_2), 33.0 (CH_2), 33.6 (CH_2), 36.8 (CH_2), 129.7 (C), 134.0 (C), 137.0 (CH), 140.1 (C); IR (neat, cm^{-1}) 2955, 2857, 1669, 1465, 1246, 1071, 835; GC-MS (EI) *m/z* (relative intensity) 348 (6) [M^+], 269 (5), 333 (1), 275 (4), 263 (3), 219 (1), 135 (2), 85 (2), 73 (100), 57 (4), 43(5); HRMS (EI) *m/z* calcd for $C_{23}H_{44}Si$ [M]$^+$ 348.3212, found 348.3243

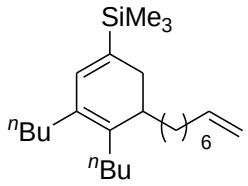
(3,4-Dibutyl-5-octylcyclohexa-1,3-dienyl)trimethylsilane (**4j**)**:** colorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.79-0.87 (m, 9H), 1.19-1.47 (m, 22H), 1.67-2.29 (m, 7H), 5.92 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -1.3 ($Si(CH_3)_3$), 15.08 (CH_3), 15.09 (CH_3), 15.10 (CH_3), 23.66 (CH_2), 23.7 (CH_2), 24.0 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 30.3 (CH_2), 30.6 (CH_2), 30.8 (CH_2), 31.7 (CH_2), 32.2 (CH_2), 32.9 (CH_2), 33.0 (CH_2), 35.3 (CH_2), 36.7 (CH),

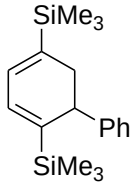
129.7 (C), 134.0 (C), 137.0 (CH), 140.2 (C); IR (neat, cm^{-1}) 2955, 2858, 1571, 1465, 1378, 1246, 1072; GC-MS (EI) *m/z* (relative intensity) 376 (5)[M^+], 361 (1), 303 (4), 263 (3), 135 (1), 73 (100), 57(5); HRMS (EI) *m/z* calcd for $C_{25}H_{48}Si$ $[M]^+$ 376.2525, found 376.3531.

(3,4-Dibutyl-5-(oct-7-enyl)cyclohexa-1,3-dienyl)trimethylsilane (**4k**)**:** colorless liquid



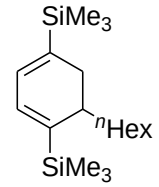
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.85 (m, 6H), 1.14-1.38 (m, 18H), 1.68-2.25 (m, 9H), 4.86 (dt, *J*=10.2, 1.7 Hz, 1H), 4.92 (dt, *J*=15.7, 1.7 Hz, 1H), 5.74 (tt, *J*=12.2, 5.2 Hz, 1H); 5.95 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -1.3 ($Si(CH_3)_3$), 15.10 (CH_3), 15.11 (CH_3), 23.7 (CH_2), 24.0 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 29.85 (CH_2), 29.89 (CH_2), 30.1 (CH_2), 30.7 (CH_2), 31.7 (CH_2), 32.2 (CH_2), 33.0 (CH_2), 33.5 (CH_2), 34.8 (CH_2), 36.7 (CH), 115.1 (CH_2), 129.7 (C), 132.4 (C), 134.0 (C), 137.0 (CH), 140.2 (CH); IR (neat, cm^{-1})3076, 2855, 1929, 1819, 1641, 1570, 1464, 1377, 1246, 1071, 835; GC-MS (EI) *m/z* (relative intensity) 375 (5) [M^+], 300 (2), 278 (17), 73 (100), 57 (2), 44 (17), 18(27); HRMS (EI) *m/z* calcd for $C_{25}H_{46}Si$ $[M]^+$ 374.3369, found 374.3403

1-(2,5-Bis(trimethylsilyl)cyclohexa-2,4-dienyl)benzene **5a:** colorless liquid



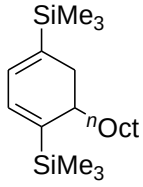
^{1}H-NMR (400 MHz, $CDCl_3$) δ -0.39 (s, 9H),-0.19 (s, 9H), 2.13 (d, *J* = 16.2 Hz, 1H), 2.32 (d, *J* = 16.5, 3 Hz, 1H), 3.23 (d, *J* = 9.2, 2 Hz,1H), 5.84 (d, 1H), 6.20 (d, 1H), 6.84-7.02 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -2.6 ($Si(CH_3)_3$), -1.7 ($Si(CH_3)_3$), 33.5 (CH_2), 41.0 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 133.6 (CH), 134.9 (CH), 136.1 (C), 143.1 (C), 146.0, (C), IR (neat, cm^{-1}) 2954, 2896, 1946, 1681, 1600, 1491, 1403, 1268, 1069, 1031, 998; GC-MS (EI) *m/z* (relative intensity) 300 (7) [M^+], 285 (3), 226 (26), 135 (10), 73 (100), 58 (3), 45 (14), 12(1); HRMS (EI) *m/z* calcd for $C_{18}H_{28}Si_2$ $[M]^+$ 300.1730, found 300.1728

5-Hexyl-1,4-bis(trimethylsilyl)cyclohexa-1,3-diene (**5i**)**:** colorless liquid



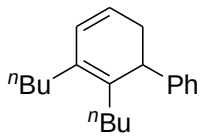
^{1}H-NMR (400 MHz, $CDCl_3$) δ -2.15(s, 9H),-1.31 (s, 9H), 0.76-0.80 (t, *J* = 6.9 Hz, 3H), 1.16-1.45 (m, 10H), 2.05-2.27 (m, 3H), 6.08 (s, 2H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ -2.5 ($Si(CH_3)_3$), -1.3 ($Si(CH_3)_3$), 14.1 (CH_3), 22.7 (CH_2), 27.5 (CH_2), 27.9 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 33.0 (CH_2), 131.0 (CH), 131.7 (CH),138.4 (C), 145.6 (C), IR (neat, cm^{-1})2954, 2851, 1608, 1461, 1236, 1071, 831; GC-MS (EI) *m/z* (relative intensity) 308 (4) [M^+], 235 (2), 219 (32), 135 (55), 75 (4), 73 (100), 59 (7); HRMS (EI) *m/z* calcd for $C_{18}H_{36}Si_2$ $[M]^+$ 308.2356, found 308.2386

1,4-Bis(trimethylsilyl)-5-octylcyclohexa-1,3-diene (**5j**)**:** colorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.03 (s, 9H), 0.79-0.83 (t, J = 6.6 Hz, 3H), 0.06-1.19 (m, 14H), 2.07-2.29 (m, 3H), 6.11 (s, 2H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ -2.5 ($Si(CH_3)_3$), -1.3 ($Si(CH_3)_3$), 14.1 (CH_3), 22.7 (CH_2), 27.5 (CH_2), 27.9 (CH_2), 29.3 (CH_2), 29.33 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 33.0 (CH_3), 131.0 (CH), 131.6 (CH),138.4 (C), 145.5 (C), IR (neat, cm^{-1})2929, 2855, 1601, 1439, 1244, 1078, 843; GC-MS (EI) *m/z* (relative intensity) 336 (4) [M^+], 321 (2), 263 (1), 223 (2), 75 (4), 73 (100), 45 (7), 18(2); HRMS (EI) *m/z* calcd for $C_{20}H_{40}Si_2$ $[M]^+$ 336.2669, found 336.2660

1-(2,3-Dibutylcyclohexa-2,4-dienyl)benzene (**7**)**:** colorless liquid



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38-0.42 (t, J = 6.9 Hz, 3H), 0.47-0.51 (s, J = 7.1 Hz,3H), 0.82-1.16 (m, 8H), 1.66-1.86 (m, 4H), 2.21 (s, 2H), 2.87 (d, 1H), 5.02 (s, 1H), 5.44 (s, 1H), 6.71-6.78 (m, 5H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 14.1 (CH_3), 22.89 (CH_2), 22.91 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 31.7 (CH_2), 32.0 (CH_2), 32.5 (CH_2), 41.8 (CH), 121.4 (CH), 126.1 (CH), 128.0 (CH), 128.1 (CH), 128.9 (C), 131.1 (C), 133.8 (C), 143.8 (C), IR (neat, cm^{-1})3026, 2872, 1944, 1668, 1492, 1072, 837; GC-MS (EI) *m/z* (relative intensity) 268 (24) [M^+], 211 (50), 155 (100), 91 (43), 79(5), 77 (6), 57 (46), 29 (11); HRMS (EI) *m/z* calcd for $C_{20}H_{28}$ $[M]^+$ 336.2191, found 268.2205

3-5. Reference

(1) For reviews: (a) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev*. **2010**, *39*, 2791. (b) Chopude, P. R.; Louie, J. *Adv. Synth. Catal*. **2006**, *348*, 2307. (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J.* Org. Chem. **2005**, 4741. (d) Yamamoto, Y. *Curr. Org. Chem*. **2005**, *9*, 503. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev*. **2004**, *104*, 2127. (f) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (g) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (h) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R, J, *Chem. Rev*. **1996**, *96*, 635. (i) Negishi, E.; Copéret, C.; Ma, S.; Liou, S,-Y.; Liu, F. *Chem. Rev*. **1996**, *96*, 365. (j) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev*. **1996**, *96*, 49.(k) Vollhardt, K, P, C. *Angew. Chem., Int. Ed*. **1984**, *23*, 539.

(2) Example of Zr-mediated cycloaddition of three different alkynes: Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc*. **1998**, 120, 1672. (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc*. **1999**, 121, 11093.

(3) Example of Ru-catalyzed cycloaddition of three different alkynes: Ura, Y.; Sato, Y.; Tsujita, H.; Kondo, T.; Imachi, M.; Mitsudo, T. *J. Mol. Catal. A: Chemical* **2005**, *239*, 166 and references therein.

(4) (a) Dienes in the Diels-Alder Reaction; Fringuelli, F.; Taticchi, A. Eds.; John Wiley: New York. 1990. (b) Aouf, C.; Abed, D, El.; Giorgi, M.; Santelli, M. *Tetrahedron Lett.* **2008**, *49*, 4630. (c) Boyd, D, R.; Sharma, N. D.; Llamas, N. M.; O'Dowd, C, R.; Allen C. C. R. *Org. Biomol. Chem.* **2006**, *4*, 2208. (d) Nguyen, R.-V.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 17184. (e) Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552. (f) Miller, C, A.; Batey, R, A.; *Org. Lett.* **2004**, *6*, 699. (g) Abbott, A, P.; Capper, G.; Davies, D, L.; Rasheed, R, K.; Tambyrajah, V. *Green Chem.*, **2002**, *4*, 24. (h) DeCosta, D, P.; Howell, N.; Pincock, A, L.; Pincock, J, A.; Rifai, S. *J. Org. Chem.* **2000**, *65*, 4698. (i) Thorarensen, A.; Palmgren, A.; Itami, K.; Bäckvall, J, -E. *Tetrahedron Lett.* **1997**, *38*, 8541. (j) Hartsough, D.; Schuster, G, B, *J. Org. Chem.* **1989**, *54*, 3 and references therein.

(5) For example, (a) Heiser, D, E.; Okuda, J.; Gambarotta, S.; Müelhaupt, R. *Macromol. Chem. Phys.* **2005**, *206*, 195. (b) Natori, I. *Macromolecules.* **1997**, *30*, 3696. (c) Chen, K.-F.; Hsu, Y.-C.; Wu, Q.; Yeh, M.-P. P.; Sun, S.-S. *Org. Lett.* **2009**, *11*, 377. (d) Natori, I.; Natori, S.; Sato, H. *Polymer*, **2006**, *47*, 7123. (e) Quirk, R.; You, F.; Wesdemiotis, C.; Arnould, M. A. *Macromolecules* **2004**, *37*, 1234 and references therein.

(6) (a) Lautens, M.; Ma, S.; Belter, R, K.; Chiu, P.; Leschziner, A. *J. Org. Chem.* **1992**, *57*, 4065. (b) Berchtold, G, A.; Ciabattoni, J.; Tunick, A, A. *J. Org. Chem.* **1965**, *30*, 3679. (c) Dyachenko, V, D.; Dyachenko, A, D.; Chernega, A, N. Russ. *J. Org. Chem.* **2004**, *40*, 397. (d) Weisz, A.; Mandelbaum, A. *J. Org. Chem.* **1984**, *49*, 2648. (e) Lasnier, G.; Wiemann, J. C. R. *Seances Acad. Sci. Ser. C.* **1969**, *268*, 1891 (f) Zupancic, B, G.; Wucherpfennig, W. *Chem. Ber.* **1967**, *100*, 1764.(g) Peppers, B, P.; Kulkarni, A, A.; Diver, S, T. *Org. Lett.* **2006**, *8*, 2539. (h) Middleton, M, D.; Diver, S, T. *Tetrahedron Lett.* **2005**, *46*, 4039. (i) Brandänge, S.; Leijonmarck, H. *Chem. Commun.* **200**4, *292*.

(7) (a) Balaich, G, J.; Rothwell, I, P. *J. Am. Chem. Soc.* **1993**, *115*, 1581. (b) Johnson, E, S.; Balaich, G, J.; Rothwell, I, P. *J. Am. Chem. Soc.* **1997**, *119*, 7685.

(8) Hilt, G.; Paul, A.; Harms, K. *J. Org. Chem.* **2008**, *73*, 5187.

(9) (a) E. J. Roskamp and S. F. Pedersen, *J. Am. Chem. Soc*, **1987**, *109*, 6551. (b) Hartung, J, B.; Pedersen, S, F. *J. Am. Chem. Soc.* **1989**, *111*, 5468. (c) Roskamp, E, J.; Dragovich, P, S.; Hartung, J, B.; Pedersen, S, F. *J. Org. Chem.* **1989**, *54*, 4736. (d) Hartung, J, B.; Pedersen, S, F. *Organometallics.* **1990**, *9*, 1414.

(10) (a) Obora, Y.; Kimura, M.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2005**, *901*. (b) Y. Obora, M. Kimura, T. Ohtake, M. Tokunaga, Y. Tsuji, *Organometallics*, **2006**, *25*, 2097.

(11) (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utinoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (b) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*,

365. (c) Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, T. *Tetrahedron Lett.* **1990**, *31*, 369. (d) Fürstner, A.; Hupperts, A.; Ptock A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215. (e) Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron*. **1992**, *48*, 3867. (f) Oshiki, T.; Nomoto, H.; Tanaka, K.;Takai, K. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 1009. (g) Du, J, A, K.; Viljoen, J, S.; Du Toit, C, J. *J. Mol. Cat*. **1991**, *64*, 269.

(12) (a) Fuchibe, K.; Mitomi, K.; Suzuki, R.; Akiyama, T. *Chem. Asian. J*. **2008**, *3*, 261. (b) Fuchibe, K.;. Oshima, Y.; Mitomi, K.; Akiyama, T. *Org. Lett*. **2007**, *9*, 1497. (c) Fuchibe, K.; Mitomi, K.; Akiyama, T. *Chem. Lett*. **2007**, *36*, 24. (d) Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc*. **2006**, *128*, 1434.

(13) (a) Obora, Y.; Takeshita, K.; Ishii, Y. *Org. Biomol. Chem*. **2009**, *7*, 428. (b) Obora, Y.; Satoh, Y.; Ishii, Y. *J. Org. Chem*. **2010**, *75*, 6046.

(14) Nelson, T, D.; Crouch, R, D. *Synthesis*. **1996**, 1031.

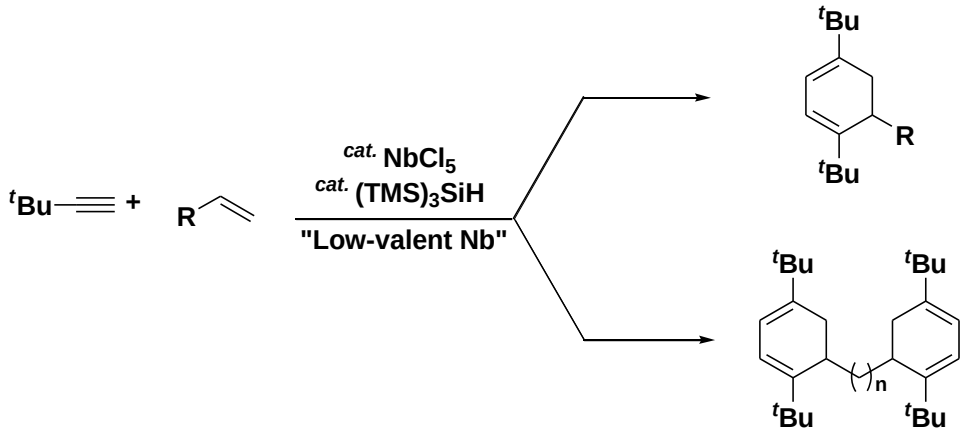
(15) Selected papers for the discussion of regioselectivity of metalacycles with alkynes, see: (a) Evans, P, A.; Sawyer, J, R.; Inglesby, P, A. *Angew. Chem. Int. Ed.* **2010**. *49*. 5746. (b) Li, S.; Qu, H.; Zhou, L.; Kanno, K.; Guo, Q.; Shen, B.; Takahashi, T. *Org. Lett*. **2009**, *11*, 3318. (c) Kanno, K.; Igarashi, E.; Zhou, L.; Nakajima, K.; Takahashi, T. *J, Am. Chem. Soc.* **2008**, *130*, 5624. (d) Saito, S.; Komagawa, S.; Azuyama, I.; Masuda, M. *J. Org. Chem*. **2007**, *72*, 9114. (f) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem. Eur. J*. **2005**, *11*, 1145. (g) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc*. **1998**, *120*, 1672. (h) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem*. **1995**, *60*, 4444. (i) Takahashi, T.; Xi, Z.; Rousset, C. J.; Suzuki, N. *Chem. Lett*. **1993**, 1001 and references cited therein.

(16) For selected examples of metal-vinyl versus metal-alkyl migratory insertion, see: (a) Wakatsuki.Y.; Aoki. K.; Yamazaki. H.; *J. Am. Chem. Soc*. **1979**. *101*. 1123. (b) Doxsee, K. M.; Mouser, J. K. M. *Organometallics*. **1990**. *9*. 3012. (c) Shibata, T.; Tahara, Y. K.; Tamura, K.; Endo, K. *J. Am. Chem. Soc*. **2008**. *130*. 3451. (d) Zhao, W; Zang, J.; *Chem. Commum*. **2010**. *46*. 7816

(17) Ura, Y. Sato, Y.; Shiotsuji, M.; Kondo, T.; Mitsudo, T.-a. *J. Mol. Catal. A: Chemical* **2004**, *209*, 35.

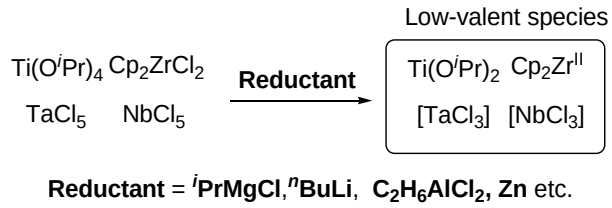
Chapter 4

Active Low-valent Niobium Catalysts from $NbCl_5$ and Hydrosilanes for Selective Intermolecular Cycloadditions



4-1. Introduction

Low-valent early transition-metal-mediated or -catalyzed organic transformations are intriguing, owing to the inherent ability of these metals to act as reductants for the activation of unsaturated compounds.[1] To date, reactions with Ti(II),[2] Zr(II),[3] Ta(III),[4] and Nb(III)[5] have been intensively studied. In general, these low-valent metals are prepared by reduction, using harsh reducing agents such as elemental metals (Na, Li, Zn), alkyllithiums, Grignard reagents, or $LiAlH_4$ (Scheme 4-1).[2-5] In general, low-valent Ti(II) and Zr(II) species are thermally unstable, and their preparation and utilization need to be performed at low temperature, hampering their practicality for use in catalytic reactions. Therefore, the development of a method for the generation of thermally stable and catalytically active low-valent early transition metals using stable, safe, and nontoxic reducing agents under mild conditions is highly desirable.

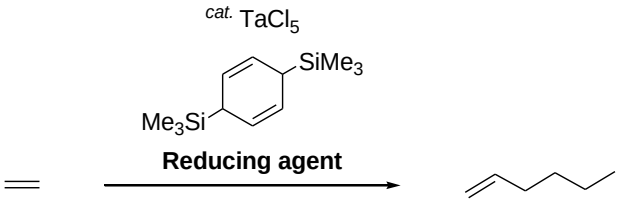


Scheme 4-1. Preparaion of low-valent early transition metal compounds

In 1987, Pedersen reported the preparation of $NbCl_3$(DME), a thermally stable low-valent early transition-metal complex, by the treatment of $NbCl_5$ with Bu_3SnH in DME.[6] This complex is currently commercially available and has been utilized as both a reagent and a catalyst in organic transformation reactions.[7] My group recently reported the $NbCl_3$(DME)-catalyzed [2 + 2 + 2] cycloaddition reaction between alkynes and alkenes, leading to 1,3-cyclohexadienes.[8]

In addition, Mashima recently reported a catalytic system consisting of $TaCl_5$ with 3,6-bis(trimethylsilyl)-1,4-cyclohexadiene (BTCD), or its methyl derivative, in the presence of ethylene led to the ethylene trimerization product (Scheme 4-2).[9]

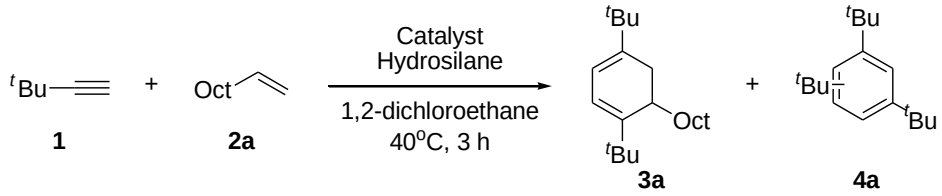
Mashima (ref. 9)



Scheme 4-2. Generation of low-valent Ta(III) from the reaction of $TaCl_5$ with BTCD

4-2. Result and Disucussion

Table 4-1. $NbCl_5$/Hydrosilane Catalyzed Reaction of *tert*-Butylacetylene (**1**) and 1-Decene (**2a**) under Various conditions[a]



Entry	Catalyst	Hydrosilane	Yield (%)[b] **3a** (Selectivity)	Yield (%)[b] **4a**
1	$NbCl_5$	$(TMS)_3SiH$	90 [88]	n.d.[d]
2	$NbCl_5$	none	n.d.[d]	[e]
3[f]	$NbCl_3$(DME)	none	61 (91:9)	14
4	$TaCl_5$	$(TMS)_3SiH$	n.d.[d]	54
5	$NbCl_5$	PMHS	74	8
6	$NbCl_5$	Et_3SiH	57 (88:12)	7
7	$NbCl_5$	$(EtO)_3SiH$	70 (53:47)	18
8	$NbCl_5$	$PhMeSiH_2$	60	trace
9	$NbCl_5$	$PhSiH_3$	58	4
10	$NbCl_5$	$(MeSiH)_2O$	84	trace
11	$NbCl_5$	$(MeSiH)_2NH$	56 (77:23)	trace
12[g]	$NbCl_5$	$(TMS)_3SiH$	73	n.d.[d]
13[h]	$NbCl_5$	$(TMS)_3SiH$	90	n.d.[d]
14[i]	$NbCl_5$	$(TMS)_3SiH$	53	n.d.[d]
15[j]	$NbCl_5$	$(TMS)_3SiH$	n.d.[d]	n.d.[d]

(a) Reaction conditions: **1** (2 mmol), **2a** (2 mmol), 1,2-dichloroethane (1 mL), $NbCl_5$ (0.2 mmol, 10 mol % based on **1**), and hydrosilane (0.2 mmol) at 40 °C for 3 h. (b) GC yields except the values in the square brackets. (c) The regioselectivity of 1,4,5-adducts was >99% unless otherwise noted. The numbers in the parentheses show the regioselectivity ratio (%) (1,4,5-adducts:1,3,5-adducts) determined by GC. (d) Not detected by GC. (e) Small amount (<5%) of amixture of intractable products including **4a** was detected by GC. f Data from ref **8a**. (g) 1 (2 mmol) and **2a** (1 mmol) were used. (h) Reaction conditions: **1** (4 mmol), **2a** (4 mmol), 1,2-dichloroethane (1 mL), $NbCl_5$ (0.1 mmol, 2.5 mol % based on **1**), and $(TMS)_3SiH$ (0.1 mmol) at 40 °C for 24 h. (i) Benzene (1 mL) was used as solvent. (j) 1,2-Dimethoxyethane (1 mL) was used as solvent.

To investigate the efficacy of the present niobium catalyst system, the reaction between *tert*-butylacetylene (**1**) and 1-decene (**2a**) was chosen as a model reaction and performed under various conditions (Table 4-1).

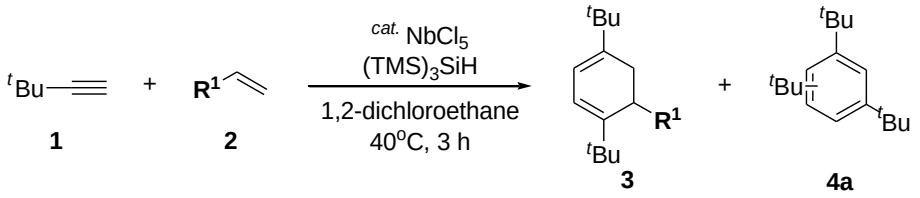
For example, an active catalyst system, consisting of the salt free reduction of $NbCl_5$ (0.2 mmol, 10 mol %) with tris(trimethylsilyl)silane ($(TMS)_3SiH$) (0.2 mmol, 10 mol %), in the presence of *tert*-butylacetylene (**1**) (2 mmol), 1-decene (**2a**) (2 mmol), and 1,2-dichloroethane (1 mL) at 40 ^oC for 3 h, produced 1,4-di-*tert*-butyl-5-octyl-1,3-cyclohexadiene (**3a**) exclusively in 90% yield with excellent chemo- and regioselectivity (Table 4-1, entry 1). The reaction led exclusively to **3a**, in preference to the formation of any tri-*tert*-butylbenzenes (**4a**), which are produced by the cyclotrimerization of alkynes[10] (1) (entry 1). It is noteworthy that when the reaction was performed in the absence of the hydrosilane, that is, with $NbCl_5$ solely, no **3a** formation was observed (entry 2), indicating that hydrosilane is a prerequisite for generating active catalyst. Furthermore, the reaction using the present catalytic system outperformed the conventionally used low-valent Nb complex, $NbCl_3$(DME), in this transformation (entry 3). When the Ta analogue, $TaCl_5$, was used combined with $(TMS)_3SiH$ under these conditions, **3a** was not obtained at all, but **4a** was preferentially obtained in 54% yield (entry 4). Screening hydrosilanes showed that those bearing bulky substituents, such as $(TMS)_3SiH$ gave the best yields of **3a**. However, besides $(TMS)_3SiH$, a variety of hydrosilanes such as polymethylhydrosiloxane (PMHS), Et_3SiH, $(EtO)_3SiH$, $PhMeSiH_2$, $PhSiH_3$, $(Me_2SiH)_2O$, and $(Me_2SiH)_2NH$ were also good reducing agents for $NbCl_5$ (entries 5-11). The best yield for **3a** was obtained when the reaction between **1** and **2a** was carried out at a 1:1 ratio. However, even when **1** and **2a** were reacted in a stoichiometric ratio (namely, **1**:**2a** = 2:1), the yield for **3a** was still good (entry 12). The reaction is remarkably effective at low catalyst loading (2.5 mol %), giving **3a** in excellent yield (entry 13). The reaction is affected by the solvent employed; halogenated solvents, such as 1,2-dichloroethane, resulted in **3a** in high yield (entry 1). Benzene could also be employed as solvent in this reaction (entry 14). However, the use of 1,2-dimethoxyethane (DME) resulted in a decrease in catalytic activity, since the DME can coordinate to the Nb metal and form stable and catalytically inert, low-valent niobium species (vide infra) (entry 15).

Under the optimized reaction conditions, as shown in Table 4-1, entry 1, the reaction of **1** with various alkenes (**2**) was examined (Table 4-2). Reactions using 1-alkenes (**2b**-**2d**) gave the corresponding 1,3-cyclohexadienes (**3b**-**3d**) in 88-93% yield, with excellent chemo and regioselectivity. Similarly, 5-methyl-1-hexene (**2e**), allylbenzene (**2f**), 4-phenyl-1-butene (**2g**), and norbornene (**2h**) were allowed to react with **1**, affording the corresponding 1,3-cyclohexadiene derivatives (**3e**-**h**) in good yield (entries 4-7).

Here, to achieve the cross-cycloaddition of alkyne and alkene, bulky *tert*-butyl acetylene (**1**) is indispensable. Thus, the use of less bulky acetylenes such as 1-hexyne and cyclohexylacetylene

exclusively lead to the alkyne cyclotrimerization products.[10]

Table 4-2. $NbCl_5/(TMS)_3SiH$ Catalyzed Reaction of **1** with Alkenes **2**[a]



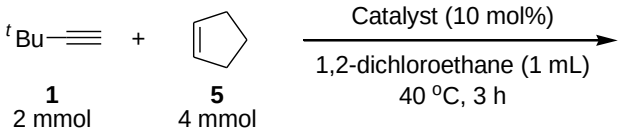
Entry	2 (R^1)	Yield (%)	
		3 (Selectivity[b])	4a
1	^{n}Bu (**2b**)	88 (**3b**)	n.d.[c]
2	^{n}Hex (**2c**)	93 (**3c**)	n.d.[c]
3	^{n}Dec (**2d**)	89 (**3d**)	n.d.[c]
4	$(CH_3)CHCH_2CH_2$ (**2e**)	77 (**3e**)	n.d.[c]
5	Bn (**2f**)	63[d] (**3f**)	10
6	$PhCH_2\ CH_2$ (**2g**)	49 (**3g**)	n.d.[c]
7	norbornene (**2h**)	99[e] (**3h**)	n.d.[c]

(a) Reaction conditions: **1** (2 mmol), **2** (2 mmol), 1,2-dichloroethane (1 mL), and $NbCl_5$ (0.2 mmol, 10 mol % based on **1** and $(TMS)_3SiH$ (0.2 mmol) at 40 °C for 3 h. (b) The regioselectivity of 1,4,5-adducts was >99% unless otherwise noted. (c) Not detected by GC. (d) A regioisomer mixture of 1,4,5- and 1,3,5-adducts in an 88:12 ratio. (e) exo,exo-Isomer was obtained exclusively.[11]

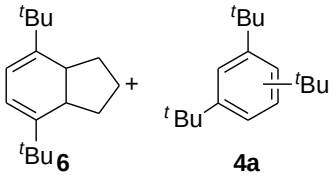
In sharp contrast to the existing $NbCl_3$(DME)-catalyzed reaction, the present $NbCl_5/(TMS)_3SiH$ catalyst system successfully achieved the cycloaddition reaction between **1** and cyclopentene (**5**) (eq 1). Thus, when the $NbCl_5/(TMS)_3SiH$ catalyst system was used for the reaction, the desired cycloaddition product, 4,7-di-*tert*-butyl-2,3,3a,7a-tetrahydro-1*H*-indene (**6**),[12] was obtained in 92% yield, along with a small amount of **4a** (5%). However, $NbCl_3$(DME) showed almost inert catalytic activity for the formation of **6**, and preferentially formed **4a** in 37% yield.

To further explore the synthetic scope and to obtain further information regarding the reactivity of this new catalyst system, the reaction of **1** with several α,ω-dienes (**7a**-**7c**) was examined (Table 4-3). The selectivity between the monocycloaddition product **8** and the dicycloaddition product **9** was controlled by the substrate ratio (**1**:**7**). Thus, when a reaction between **1** (2 mmol) and **7** (4 mmol) was performed, only a single alkene within the α,ω-diene is subjected to reaction with **1**, and the corresponding 5-ω-alkenyl-1,3-cyclohexadiene (**8**) is obtained, exclusively (entries 1-3). An almost similar catalytic activity and selectivity are observed for $NbCl_5/(TMS)_3SiH$ (entries 1 and 2) and $NbCl_3$(DME) (entry 3). However, it is noteworthy that for the reaction of **1** (2 mmol) and **7** (0.5

mmol) using the $NbCl_5/(TMS)_3SiH$ catalyst system both alkene sides of the α,ω-diene react, leading



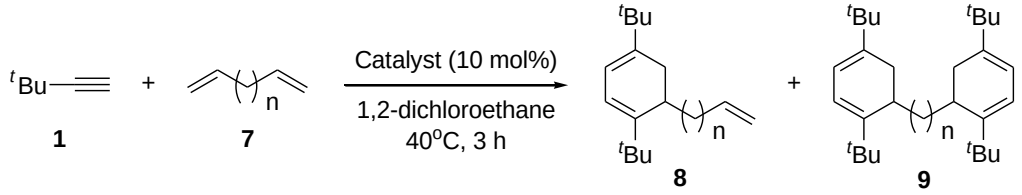
(**1**)



Catalyst	**6**	**4a**
$NbCl_5/(TMS)_3SiH$	92%	5%
$NbCl_3(DME)$	2%	37%

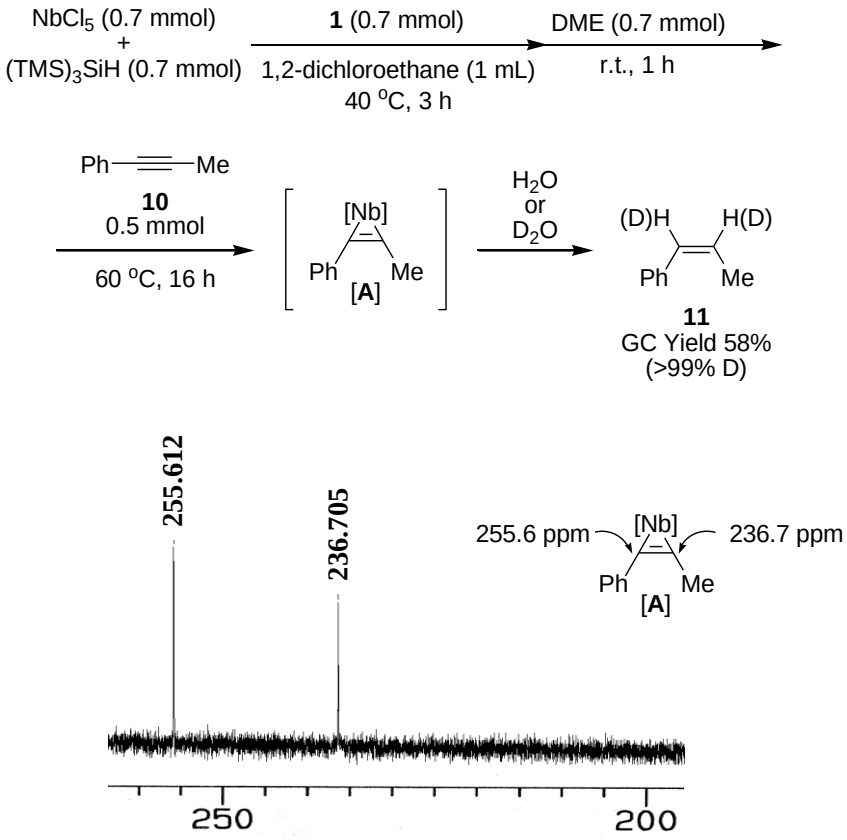
to dicycloaddition products (**9a-c**), exclusively, in high yield (entries 4-6). No **9** was obtained at all using $NbCl_3(DME)$ as catalyst. Instead, **8** formed in low yield (11%), along with the alkyne trimerization product **4a** (27%) (entry 7).

Table 4-3. Nb-Catalyzed Reaction of (**1**) with α,ω-Dienes (**7**)[a]



		7		Yield (%)	
Entry	Catalyst	n	**1**:**7** (mmol)	**8** (Selectivity)[b]	**9**
1	$NbCl_5/(TMS)_3SiH$	4	2:4	77(**8a**)	n.d.[c]
2	$NbCl_5/(TMS)_3SiH$	6	2:4	90(**8b**)	n.d.[c]
3[d]	$NbCl_3(DME)$	6	2:4	81(**8b**)[e]	n.d.[c]
4	$NbCl_5/(TMS)_3SiH$	4	2:0.5	trace	91(**9a**)
5	$NbCl_5/(TMS)_3SiH$	6	2:0.5	trace	79(**9b**)
6	$NbCl_5/(TMS)_3SiH$	8	2:0.5	trace	66(**9c**)
7[f]	$NbCl_3(DME)$	4	2:0.5	11(**8a**)[g]	n.d.[c]

(a) Reaction conditions: **1** (2 mmol), **7** (0.5-4 mmol), 1,2-dichloroethane (1 mL), $NbCl_5$ (0.2 mmol, 10 mol % based on **1**), and $(Me_3Si)_3SiH$ (0.2 mmol) at 40 °C for 3 h. (b) The regioselectivity of 1,4,5-adducts was >99% unless otherwise noted. (c) Not detected by GC. (d) Data from ref **8b**. (e) A regioisomer mixture of 1,4,5- and 1,3,5-adducts in a 92:8 ratio. (f) In addition to the product **8a**, **4a** (27%) was formed. (g) A regioisomer mixture of 1,4,5- and 1,3,5-adducts in a 95:5 ratio.



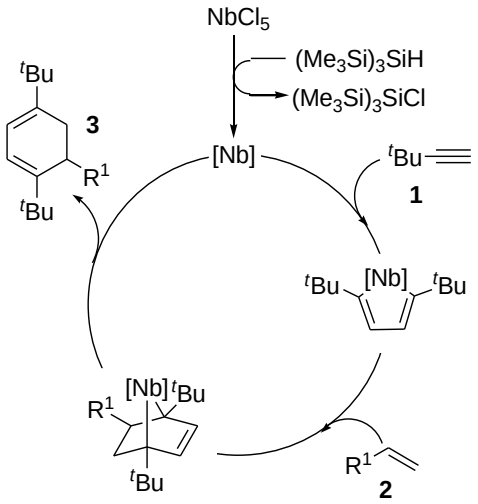
Scheme 4-3. Generation of low-valent Nb from $NbCl_5$/$(TMS)_3SiH$

The low-valent niobium species appears critical to obtain efficient catalytic activity for the present transformation.[5,8] Indeed, no cycloaddition reaction between alkyne with alkene took place using $NbCl_5$ (Nb(V)) catalyst alone. On the other hand, it is reported that the low-valent niobium complex $NbCl_3$(DME) reacts with internal alkynes to form an Nb-alkyne complex, as confirmed by hydrolysis to give the *cis*-alkene.[6,7a,7b,7d] To obtain structural information regarding the catalytically active low-valent Nb species generated from $NbCl_5$ and $(TMS)_3SiH$, we initially carried out a complexation reaction between a mixture of $NbCl_5$/$(TMS)_3SiH$ and 1-phenyl-1-propyne (**10**), under the conditions reported for the above-mentioned preparation of the Nb-alkyne complex from $NbCl_3$(DME).[6,7] However, no Nb-alkyne species was verified by hydrolysis of the reaction mixture, and **10** was evidently converted during the reaction course to give an intractable mixture of oligomeric products. This implies that the Nb species generated between $NbCl_5$ and $(TMS)_3SiH$ are too reactive for the analysis of any Nb-alkyne species in a stable form. Indeed, all attempts to isolate or fully characterize the active Nb species have been unsuccessful. However, experimental confirmation for the formation of the low-valent Nb-alkyne complexes has been achieved by adding both **1** (1 equiv) and 1,2-dimethoxyethane (DME) (1 equiv) to a reaction mixture of $NbCl_5$/$(TMS)_3SiH$ and internal alkyne (Scheme 4-3). Thus, **1** (0.7 mmol) and 1,2- dichloroethane (1

mL) was added to a mixture of $NbCl_5$ (0.7 mmol) and $(TMS)_3SiH$ (0.7 mmol). The reaction mixture was stirred at 40 °C for 3 h. Subsequently, DME (0.7 mmol) and **10** (0.5 mmol) were added, and the mixture was stirred at 60 °C for 16 h. Thereafter, the formation of an Nb-alkyne complex was verified by hydrolysis or deuteriolysis of the reaction mixture, affording *cis*-1-phenyl-1-propene (**11**) in substantial yield (>99% D incorporated after deuteriolysis). In the $^{13}C\{^1H\}$ NMR spectrum for the reaction mixture of $NbCl_5$/$(TMS)_3SiH$/DME-**10**, after the addition of benzene-d_6 at 20 °C, alkyne carbon peaks assignable to the low-valent Nb-alkyne complex [**A**] appear at 236.7 and 255.6 ppm, which agrees with the reported values for the (DME)$NbCl_3$-**10** complex (237.5 and 256.2 ppm)[7a,b]. Therefore, the addition of DME to the present highly catalytic active low-valent niobium species would actually lower the activity, resulting in a stable low-valent Nb(III) species, as found for $NbCl_3$(DME).[6,7]

Although it is not possible to confirm a detailed reaction mechanism, $NbCl_5$ could be reduced by $(TMS)_3SiH$ to form **A** (and $(TMS)_3SiCl$); presumably low-valent Nb species are generated, on the basis of the experimental data.[13]

On the basis of these experiments, we propose the reaction mechanism shown in Scheme 4-4. In this reaction pathway, the initial step is the generation of the low-valent niobium species from $NbCl_5$, in which $(TMS)_3SiH$ acts as a reducing agent. Subsquently, the reaction may then proceed via oxidative cyclometalation of the two terminal alkyne molecules (**1**) to give a niobacyclopentadiene intermediate. The subsequent reaction with an alkene would exclusively produce the desired cycloaddition product (**3**).[8,13]



Scheme 4-4. A plausible reaction mechanism

4-3. Conclusion

In summary, I have developed an approach for generating low-valent Nb(III) species, via a salt-free reduction method from $NbCl_5$/hydrosilane. These species are active catalysts for the selective [2 + 2 + 2] cycloaddition reactions of terminal alkynes and alkenes, to give 1,3-cyclohexadiene derivatives in high yield. The catalyst system shows remarkable reactivity and selectivity toward the dicycloadditions of α,ω-dienes, as well as the cycloaddition of cyclopentene, with **1**, which could not be achieved using the conventional $NbCl_3$(DME) catalyst system.

4-4. Experimental Section

General

GLC analysis was performed with a flame ionization detector using a 0.22 mm x 25 m capillary column (BP-5). ^1H, ^{13}C, and ^{29}Si NMR were measured at 400, 100, and 78.7 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. The products were characterized by ^{1}HNMR, ^{13}C NMR, HMQC and HMBC.

Typical Reaction Procedure for the Preparation of 3a (entry 1, Table 4-1).

A mixture of *tert*-butylacetylene (**1a**) (164 mg, 2 mmol), 1-decene (**2a**) (281 mg, 2 mmol), $NbCl_5$ (54 mg, 0.2 mmol), tris(trimethylsilyl)silane (50 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 3 h at 40 °C under Ar. The yields of the products were estimated from the peak areas, based on the internal standard technique using GC, and **3a** was obtained in 90% yield. The product **3a** was isolated by silica gel column chromatography (*n*-hexane as eluent) in 88% yield (268 mg) a colorless liquid.

Synthesis of 6 from 1a and 5 Using the $NbCl_5$/$(TMS)_3SiH$ Catalyst System (eq 1).

A mixture of *tert*-butylacetylene (**1**) (164 mg, 2 mmol), cyclopentene (**5**) (272 mg, 4 mmol), $NbCl_5$ (54 mg, 0.2 mmol), tris(trimethylsilyl)silane (50 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 3 h at 40 °C under Ar. The product **6** was isolated by silica gel column chromatography (*n*-hexane as eluent) in 92% yield (214 mg) as a colorless liquid.

Typical Reaction Procedure for the Preparation of 8a (Table 4-3, entry 1).

A mixture of *tert*-butylacetylene (**1**) (164 mg, 2 mmol), 1,7-octadiene (**7a**) (441mg, 4mmol), $NbCl_5$ (54 mg, 0.2 mmol), tris(trimethylsilyl)silane (50 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 3 h at 40 °C under Ar. The product **8a** was isolated by silica gel column chromatography (*n*-hexane as eluent) in 77% yield (211 mg) as a colorless liquid.

Typical Reaction Procedure for the Preparation of 9a (Table 4-3, entry 4).

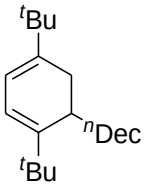
A mixture of *tert*-butylacetylene (**1**) (164 mg, 2 mmol), 1,7-octadiene (**7a**) (55 mg, 0.5 mmol), $NbCl_5$ (54mg, 0.2mmol), tris(trimethylsilyl)silane (50 mg, 0.2 mmol), and 1,2-dichloroethane (1 mL) was stirred for 3 h at 40 °C under Ar. The product **9a** was isolated by silica gel column chromatography (*n*-hexane as eluent) in 91% yield (199 mg) as a colorless liquid.

Reaction of $NbCl_5$/$(TMS)_3SiH$ with 10 (Scheme 4-3).

A solution of $NbCl_5$ (189 mg, 0.7 mmol), $(TMS)_3SiH$ (174 mg, 0.7 mmol), and *tert*-butylacetylene (**1**) (57 mg, 0.7 mmol) in 1,2-dichloroethane (1 mL) was stirred for 3 h at 40 °C under Ar. Subsequently, 1,2-dimethoxyethane (DME) (63 mg, 0.7 mmol) was added to the reaction mixture and stirred for 1 h at room temperature under Ar. Then, 1-phenyl-1-propyne (**10**) (58 mg, 0.5 mmol) was added to the reaction mixture and stirred for 16 h at 60 °C under Ar. The yields of the products were estimated from the peak areas based on the internal standard technique using GC, and **11** was obtained in 58% yield. In the $^{13}C\{^1H\}$ NMR spectrum for the reaction mixture of $NbCl_5$/$(TMS)_3SiH$/DME-**10** in benzene-d_6 at 20 °C, alkyne carbon peaks assignable to the low-valent Nb-alkyne complex [**A**] appeared at 236.7 and 255.6 ppm, which agrees with the reported values for the $NbCl_3$(DME)-**10** complex (237.5 and 256.2 ppm).

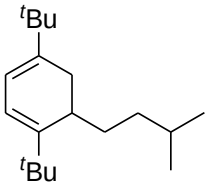
Charactarization of the compounds

1,4-Di-*tert*-butyl-5-decylcyclohexa-1,3-diene (**3d**): colorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J = 5.7 Hz, 3H), 0.97 (s, 9H), 1.06-1.25 (m, 18H), 1.32 (s, 9H), 2.01-.27 (m, 2H), 2.23, (d, J = 15Hz 1H), 5.61 (s, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 27.6 (CH_2), 28.2 (CH_2), 28.3 (CH_2), 28.5 (CH_3), 29.4 (CH_2), 29.6 (CH_3), 29.65 (CH_2), 29.68 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 33.3 (CH), 35.0 (C), 35.6 (C), 115.4 (CH), 115.6 (CH) 143.6 (C), 150.2 (C) ; IR (neat, cm^{-1}) 3065, 2924, 1647, 1597, 1465, 1359, 835; GC-MS (EI) m/z (relative intensity) 332 (6) [M^+], 277 (11), 221 (3), 191 (3), 137 (2), 91 (3), 79 (2), 57 (100), 41 (8); HRMS (EI) m/z calcd for$C_{24}H_{44}$ [M]$^+$ 332.3443, found 332.3450.

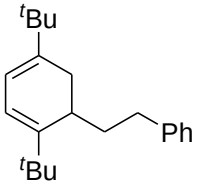
1,4-Di-*tert*-butyl-5-isopentylcyclohexa-1,3-diene **(3e)**: colorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.63-0.67 (m, 6H), 0.86 (s, 9H), 0.90 (s, 9H), 1.16-1.36 (m, 4H), 1.83-1.90 (m, 1H), 2.10, 2.14 (m, 3H), 5.50 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.0 (CH_3), 25.9 (CH_2), 28.3 (CH_2), 28.4 (CH_3), 28.5 (CH), 29.6 (CH_3), 33.9 (CH), 35.0 (C), 35.6 (C), 37.2 (CH_2), 115.3 (CH), 115.6 (CH), 143.7 (C), 150.2 (C); IR (neat, cm^{-1}) 3055, 2955, 1645, 1597, 1466, 1367, 1265, 837; GC-MS (EI) m/z (relative intensity) 262 (14) [M^+], 247 (2), 191 (2), 135 (2), 79 (2),

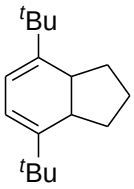
57(100), 43(4). HRMS (EI)m/z calcd for $C_{19}H_{34}$ $[M]^+$ 262.2661, found 262.2663.

1-(2-(2,5-Di-*tert*-butylcyclohexa-2,4-dienyl)ethyl)benzene (**3g**): colorless liquid



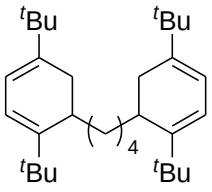
^{1}H-NMR(400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.03 (s, 9H), 1.79-1.86 (m, 2H), 2.08-2.41 (m, 2H), 2.34 (d, J = 15.2 Hz, 1H), 2.62 (t, J = 7.1 Hz, 2H), 5.62 (s, 2H), 7.05-7.19 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.1 (CH_2), 28.6 (CH_3), 29.5 (CH_3), 30.4 (CH_2), 32.8 (CH), 34.0 (CH_2), 35.0 (C), 35.6 (C), 115.8 (2CH), 125.6 (CH), 128.2 (CH), 128.4 (CH), 142.6 (C), 143.4 (C), 149.6 (C); IR (cm^{-1}) 3018, 2964, 2041, 1602, 1463, 1367, 1217, 1029, 929, 725; GC-MS (EI) m/z (relative intensity) 296 (13) $[M]^+$, 192 (2), 135 (2), 105 (7), 91 (12), 77(2), 57(100), 41(12). Anal. Calcd for $C_{22}H_{32}$: C, 89.12; H, 10.88. Found: C, 88.84; H, 10.94.

4,7-Di-*tert*-butyl-2,3,3a,7a-tetrahydro-1H-indene (**6**): colorless liquid



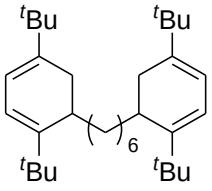
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 18H), 1.24-1.86 (m, 6H), 2.51-2.56. (m, 2H), 5.63 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_2), 30.3 (CH_3), 33.5 (CH_2), 35.6 (C), 42.8 (CH), 116.1 (CH), 147.1 (C); IR (cm^{-1}) 3057, 2951, 1463, 1360, 1248, 1198, 851; GC-MS (EI) m/z (relative intensity) 232 (19) $[M^+]$, 217 (18), 175 (17), 119 (15), 79 (3), 57 (100), 41 (17). HRMS (EI) m/z calcd for $C_{17}H_{28}$ $[M]^+$ 232.2191, found 232.2200

1,4-Bis(2,5-di-*tert*-butylcyclohexa-2,4-dienyl)butane **9a**: white solid, mp 65-67 ^{o}C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 18H), 0.89 (s,18H), 1.10-1.19 (m, 8H), 1.84-2.12 (m, 6H), 5.49 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.3 (CH_2), 28.5 (CH_3), 29.6 (CH_3), 31.6 (CH_2), 33.0 (CH), 33.51 (CH_2), 35.0 (C), 35.6 (C), 115.45 (CH), 115.53 (CH), 143.5 (C), 150.5 (C); IR (KBr, neat, cm^{-1}) 3057, 2964, 1645, 1463, 1360, 1265, 833; GC-MS (EI) m/z (relative intensity) 438 (5) $[M^+]$, 382 (4), 248 (2), 218 (2), 192 (30), 79 (2), 57 (100), 41(22). HRMS (EI) m/z calcd for $C_{32}H_{54}$ $[M]^+$ 438.4226, found 438.4222.

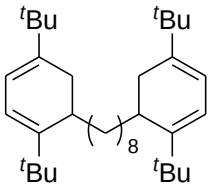
1,6-Bis(2,5-di-*tert*-butylcyclohexa-2,4-dienyl)hexane (**9b**): white solid, mp 76-78 ^{o}C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 18H), 0.95 (s, 18H), 1.11-1.20 (m, 8H), 1.30-1.42 (m, 4H), 1.90-2.20 (m, 6H), 5.55 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.6 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 28.5 (CH_3), 29.6 (CH_3), 31.6 (CH_2), 33.3 (CH), 35.0 (C), 35.6 (C), 115.4 (CH), 115.6 (CH), 143.5 (C), 150.2 (C); IR (KBr, neat, cm^{-1}) 3053, 2964, 1647, 1597, 1463, 1359, 1265, 1198, 837; GC-MS (EI) m/z (relative intensity) 466 (5) $[M^+]$, 353 (1), 207 (1), 175 (4), 131 (1), 91 (2), 57 (100),

41 (6). HRMS (EI) m/z calcd for C34H58 $[M]^+$ 466.4539, found 466.4529.

1,8-Bis(2,5-di-*tert*-butylcyclohexa-2,4-dienyl)octane (**9c**): white solid, mp 85-88 °C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 18H), 0.96 (s, 18H), 1.11-1.49 (m, 16H), 1.90-2.20 (m, 6H), 5.55 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 28.5 (CH3), 29.6 (CH_3), 29.8 (CH_2), 31.6 (CH_2), 33.2 (CH), 35.0 (C), 35.6 (C), 115.3 (CH), 115.5 (CH), 143.6 (C), 150.2 (C); IR (KBr, neat, cm^{-1}) 2964, 2853, 2368, 1473, 1359, 1265, 1195, 835; GC-MS (EI) m/z (relative intensity) 494 (4) $[M]^+$, 437 (1), 381 (2), 191 (1), 175 (4), 91 (2), 57 (100), 41 (5). HRMS (EI) m/z calcd for $C_{36}H_{62}$ $[M]^+$ 494.4852, found 494.4874

4-5. Reference

(1) (a) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev*. **2000**, *100*, 2835. (b) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 755. (c) Negishii, E.; T. Takahashi, *Acc. Chem. Res*. **1994**, *27*, 124. (d) Kulinkovich, O. G.; Meijere, A. de.; *Chem. Rev*. **2000**, *100*, 2835.

(2) (a) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696. (b) Kawaji, T.; Shohji, N.; Miyashita, K.; Okamoto, S. *Chem. Comm*. **2011**, *47*, 7857. (c) Razus, A. C.; Dragu, E. A.; Nica, S.; Nicolescu, A. *Tetrahedron Lett*. **2011**, *52*, 1858. (d) Fukuhara, K.; Okamoto, S.; Sato, F.; *Org. Lett*. **2003**, *5*, 2145. (e) Lysenko, I. L.; Hyung, K. K.; Lee, G.; Cha, J. K. *J. Am. Chem. Soc*, **2008**, *130*, 15997. (f) Tarselli, M. A.; Micalizio, G. C. *Org. Lett*. **2009**, *11*, 4596. (g) Hanamoto, T.; Yamada, K. *J. Org. Chem*. **2009**, *74*, 7559. (h) Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc*. **1993**, *115*, 1581. (i) Johnson, E. S.; Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc*. **1997**, *119*, 7685.

(3) (a) Takahashi, T.; Tsai, F. –Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc*. **1999**, *121*, 11093. (b) Kanno, K.; Igarashi, E.; Zhou, L.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc*. **2008**, *130*, 5624. (c) Wang, G.; Negishi, E. *Eur. J. Org. Chem*. **2009**, 1679. (d) Nishihara, Y.; Miyasaka, M. Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc*. **2007**, *129*, 12634. (e) Xu, Z.; Negishi, E. *Org. Lett*. **2008**, *10*, 4311.

(4) (a) Shimizu, H.; Kobayashi, S. *Tetrahedron Lett*. **2005**, *46*, 7593. (b) Oshiki, T.; Tanaka, K.; Yamada, J.; Ishiyama, T.; Kataoka, Y.; Mashima, K.; Tani, K.; Takai, K. *Organometallics*, **2003**, *22*, 464. (c) Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett*. **1995**, 851. (d) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem. Int. Ed*. **2002**, *41*, 1389. (e) Brennessel, W. W.; Ellis, J. E.; Pomije, M. K.; Sussman, V. J.; Urnezius, E.; Young, V. G., Jr. *J. Am. Chem. Soc*. **2002**, *124*, 10258.

(5) (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem*. **1992**, *57*, 1973. (b) Fuchibe, K.; Akiyama, T.; *J. Am. Chem. Soc*. **2006**, *128*, 1434. (c) Arai, S.; Takita, S.; Nishida, A. *Eur. J. Org. Chem*. **2005**, 5262. (d) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *Tetrahedron*

Lett. **1990**, *31*, 365. (e) Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, K. *Tetrahedron Lett.* **1990**, *31*, 369. (f) Oshiki, T.; Nomoto, H.; Tanaka, K.; Takai, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1009.

(6) (a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551.

(7) (a) Obora, Y.; Kimura, M.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2005**, 901. (b) Obora, Y.; Kimura, M.; Ohtake, T.; Tokunaga, M.; Tsuji, Y. *Organometallics*, **2006**, *25*, 2097. (c) Hartung, J. B., Jr.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 5468. (d) Roskamp, E. J.; Dragovich, P. S.; Hartung, J. B., Jr.; Pedersen, S. F. *J. Org. Chem.* **1989**, *54*, 4736. (e) Hartung, J. B., Jr.; Pedersen, S. F. *Organometallics* **1990**, *9*, 1414. (f) Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron* **1992**, *48*, 3867. (g) Bruno, J. W.; Li, X. J. *Organometallics* **2000**, *19*, 4672.

(8) (a) Obora, Y.; Takeshita, K.; Ishii, Y. *Org. Biomol. Chem.* **2009**, *7*, 428. (b) Obora, Y.; Satoh, Y.; Ishii, Y. *J. Org. Chem.* **2010**, *75*, 6046. (c) Satoh, Y.; Obora, Y. *Org. Lett.* **2011**, *13*, 2568.

(9) Müller, R. A.; Tsurugi, H.; Saito, T.; Yanagawa, M.; Oda, S.; Mashima, K. *J. Am. Chem. Soc.* **2009**, *131*, 5370.

(10) For recent reviews, see: (a) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (b) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. and references therein.

(11) Craig, D. C.; Oliver, A. M.; Paddon-Row, M. N. *J. Chem, Soc, Perkin Trans 1* **1993**, 197.

(12) The stereochemistry of **6** was not determined.

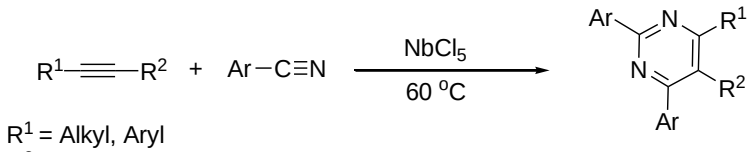
(13) The ^{29}Si-NMR(DEPT) measurement of the reaction mixture of $NbCl_5$ and $(TMS)_3SiH$ showed peaks at -11.3 and -13.4 ppm assignable to $(TMS)_3SiCl$ as well as -83.2 and -12.5 ppm (lit[14]: -85.2 and -12.9 ppm) assignable to *t*-BuCH=CH$(TMS)_3$ (**12**). Although the role of the bulky substituent on hydrosilane (such as $(TMS)_3SiH$) in the present catalytic system is unclear at present, the **12** may coordinate with the Nb center, increasing the effectiveness of the catalysis.

(14) Naka, A.; Ohnishi, H.; Oshita, J.; Ikadai, J.; Kunai, A.; Ishikawa, M. *Organometallics* **2005**, *24*, 5356.

(15) Cadierno, V.; Garcia-Garrido, S, E.; Gimeno, J. *J. Am. Chem. Soc.* **2006**, *128*, 1509.

Chapter 5

Strategy for the Synthesis of Pyrimidine Derivatives: $NbCl_5$-mediated Cycloaddition of Alkynes and Nitriles



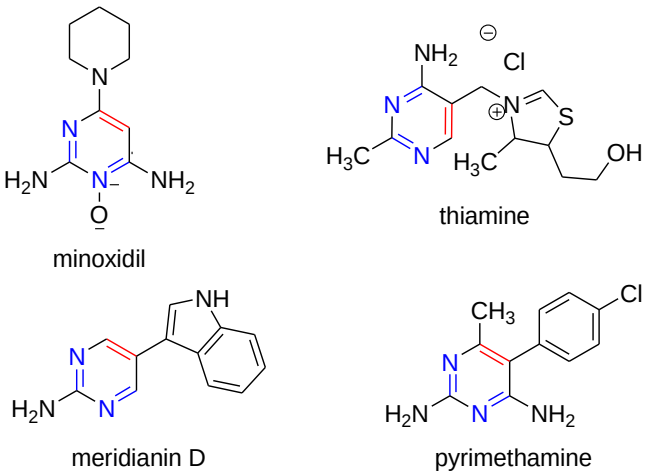
R^1 = Alkyl, Aryl
R^2 = Alkyl, H

5-1. Introduction

Pyrimidine derivatives are one of the most important class of azaheterocyclic compounds.[1] Pyrimidine derivatives are key structures in many natural products and biologically active substances, including minoxidil, thiamine, meridianin D, and pyrimethamine (Scheme 5-1).[1] In addition, some pyrimidines are used in polymer and supramolecular chemistry.[2,3] These compounds have therefore attracted much attention from synthetic chemists for use in efficient syntheses.[4,5]

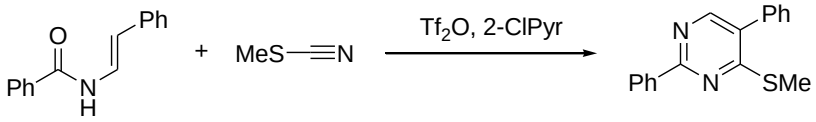
Since Brugnatelli synthesized pyrimidines,[4a] many synthetic organic chemists have studied preparations of pyrimidine derivatives. Many of the reported reactions are synthetic methods that do not use transition metals, such as condensations of N−C−N fragments and ketones, condensations of formamidine acetate with ketones,[4b] and reactions of *N*-vinylamides with nitriles (Scheme 5-2).[4c] Various other synthetic methods for the synthesis of pyrimidine derivatives have been reported, such as transition-metal-mediated or -catalyzed condensation reactions of amidines with propargylic alcohols[5a] and three-component coupling reactions of functionalized enamines, triethyl orthoformate, and potassium aryltrifluoroborates with pyrimidine chlorides.[5d]

Intermolecular cycloaddition of one alkyne molecule and two nitrile molecules is one of the simplest and atom-economical methods for preparing pyrimidine derivatives. Previously, Martinez, Hanack, and co-workers reported the reaction of alkynes and nitriles to give trisubstituted pyrimidine derivatives by using a strong acid such as CF_3SO_3H .[4h]



Scheme 5-1. Biologically active compounds

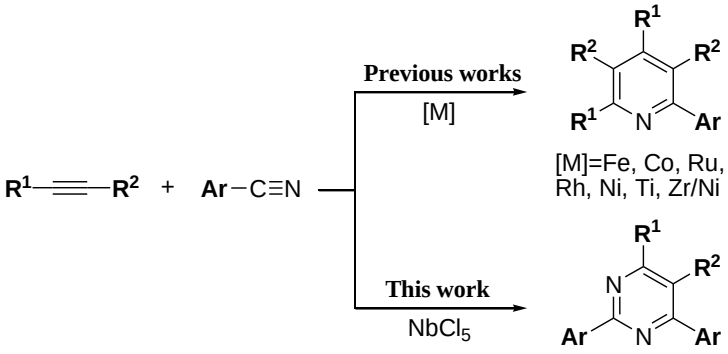
Movassaghi (ref 4c)



Scheme 5-2. The direct condensation pf cyanic acids with *N*-vinyl/aryl amides

Alternatively, transition-metal-mediated/-catalyzed [2+2+2] intermolecular cycloaddition of alkynes and nitiriles is one of the most efficient, simple, and atom-economical methods for preparing pyrimidine derivatives. However, such a cycloaddition reaction exclusively afforded pyridines, not pyrimidines (Scheme 5-3, previous work).[6]

Recently, we reported that low-valent Nb catalysts ($NbCl_3$(DME)[7] and $NbCl_5$/hydrosilane system[8d]) are useful for cycloaddition reactions of terminal alkynes, internal alkynes, and alkenes to give 1,3-cyclohexadienes.[8]



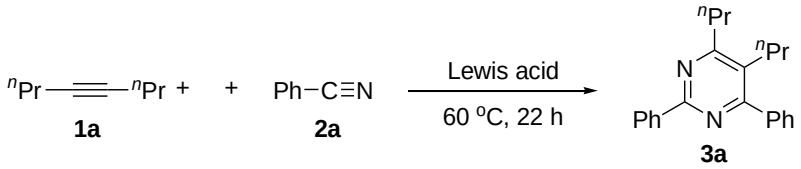
Scheme 5-3. Transition-metal-catalyzed or -mediated reactions of alkynes and nitriles

5-2. Result and Discussion

Initially I select 4-octyne (**1a**) and benzonitrile (**2a**) as model substrates and carried out intermolecular cycloaddition reactions using various transition-metal catalysts (Table 5-1). For example, **1a** (1 mmol) was reacted with **2a** (2 mmol) in the presence of $NbCl_5$ (0.2 mmol) in 1,2-dichloroethane (1 mL) at 60 °C for 22 h. 2,4-Diphenyl-5,6-*n*-dipropylpyrimidine (**3a**) was obtained in 10% yield with excellent chemoselectivity (Table 5-1, entry 1). When 2 mL of **2a** was used instead of 1,2- dichloroethane, **3a** was obtained in 21% yield (entry 2).

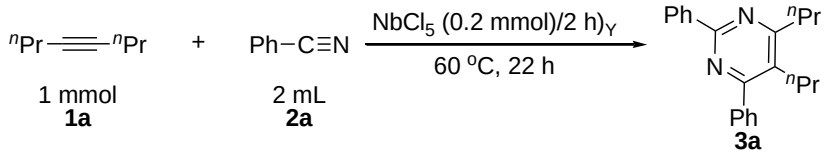
To optimize the reaction, I compared $NbCl_5$ with different metal salts (NbF_5, $TaCl_5$, $ZrCl_4$, $AlCl_3$, $FeCl_3$, and $CeCl_3$) (entries 3−8). The catalyst precursor significantly influenced the reaction activity. The best results for the model cycloaddition reaction were observed in the presence of an $NbCl_5$ catalyst. I tried to increase the yield of **3a**. In one of many attempts, I tried a stoichiometric reaction; this gave **3a** in 50% yield (entry 9). I succeeded in obtaining **3a** in 86% yield by adding $NbCl_5$ (0.2 mmol) to the reaction mixture six times every 2 h (entry 10, Scheme 5-4). Surprisingly, 1,2,3,4,5,6-hexapropylbenzene from cyclotrimerization of 4-octyne was not formed in the present reaction.[9] Here, low-valent Nb compounds such as $NbCl_3$(DME)[7,8]did not afford **3a** at all under these conditions.

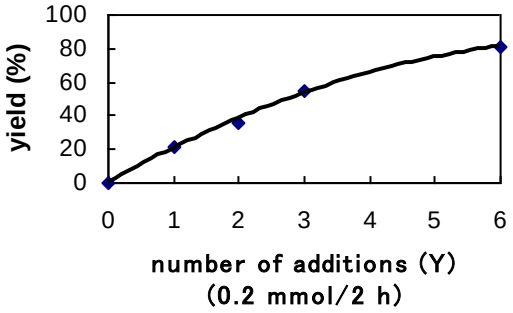
Table 5-1. Optimization of Model Reaction. [a]



Entry	Lewis acid (amt (equiv))	Yield of **3a** (%)[b]
1[c]	$NbCl_5$ (0.2)	10
2	$NbCl_5$ (0.2)	21
3	NbF_5 (0.2)	12
4	$TaCl_5$ (0.2)	9
5	$ZrCl_4$ (0.2)	trace
6	$AlCl_3$ (0.2)	12
7	$FeCl_3$ (0.2)	trace
8	$CeCl_3$ (0.2)	n.d. [d]
9	$NbCl_5$ (0.2)	50
10[e]	$NbCl_5$ (0.2)	86 (79)

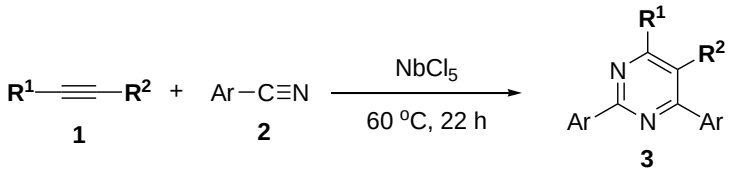
(a) Reaction conditions: **1a** (1 mmol), **2a** (2 mL) and Lewis acid (amount based on **1a**) at 60 °C for 22 h under Ar (entries 2−8). (b) GC yields except for the value in the parentheses. (c) Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), and $NbCl_5$ (0.2 mmol) in 1,2-dichloroethane (1 mL) at 60 °C for 22 h under Ar. (d) Not detected by GC. (e) The reaction was performed by adding $NbCl_5$ (0.2 mmol) in six portions every 2 h over 22 h ($(0.2\ mmol/2\ h)_6$).



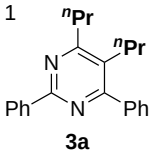
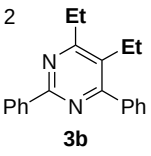
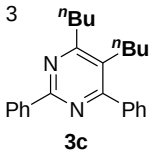
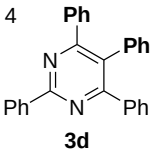
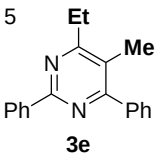
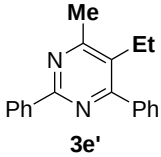
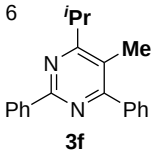
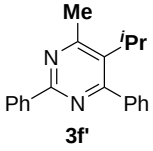
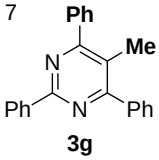
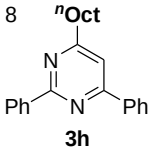
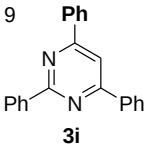
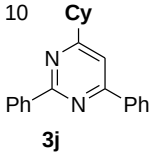
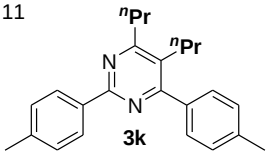
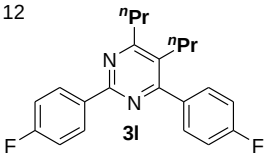


Scheme 5-4 Effect of number of additions

Table 5-2. Scope of Reaction of Alkynes **1** with Aryl Nitriles **2**[a]



1 2 **3**

Entry			
	Yield of **3** (%)[b]		
1  **3a**	2  **3b**	3  **3c**	
79	72	82	
4  **3d**	5  **3e**	 **3e'**	
n.d.[c]	75(**3e**:**3e'**=61:39)		
6  **3f**	 **3f'**	7  **3g**	
75(3f:3f'=61:39)		76	
8  **3h**	9  **3i**	10  **3j**	
74(>95)[d]	50	57	
11  **3k**	12  **3l**		
57	39		

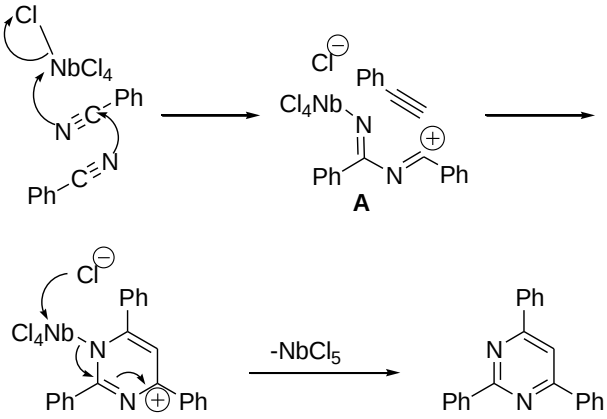
(a) Reaction conditions: see optimized conditions (Table 5-1, entry 10). (b) Isolated yields. (c) Not detected by GC. (d) The values in parentheses show the selectivity (%) of 2,4,6-substituted adducts.

Under the optimized reaction conditions, i.e., Table 5-1, entry 10, we investigated the scope of the reaction using various alkynes and nitriles (Table 5-2). For example, the internal alkynes 4-octyne

(**1a**), 3-hexyne (**1b**), and 5-decyne (**1c**) participated in the reaction and the corresponding pyrimidine derivatives (**3a**−**c**) were obtained in 72−82% isolated yields with excellent chemo and regioselectivities (entries 1−3). However, the reaction with diphenylacetylene (**1d**) did not afford any of the corresponding pyrimidine (**3d**; entry 4). The regioselectivities of the desired pyrimidines from the reactions of unsymmetrical alkynes (**1e**−**g**) and **2a** were influenced by electronic effects on the unsymmetrical internal alkynes (entries 5−7). For instance, 2-pentyne (**1e**) and 4-methyl-2-pentyne (**1f**) gave the corresponding products in good yields as a mixture of regioisomers (**3e**,**f** and **3e′**,**f′**); these pyrimidines were characterized by ^{1}H and ^{13}C-NMR spectroscopy, and the resonances were assigned using 2D-HMQC and HMBC. However, when 1-phenyl-1-propyne (**1g**) was used, **3g** was obtained in 76% yield with >99% regioselectivity. The reactions of trimethylsilylacetylene and ethyl propiolate did not afford the products **3**.

I next examined the scope of the reaction with terminal alkynes. The reaction was successful using terminal alkynes with *n*-octyl, phenyl, and cyclohexyl groups. The terminal alkynes 1-decyne (**1h**), phenylacetylene (**1i**), and cyclohexylacetylene (**1j**) gave the corresponding desired products (**3h**−**j**) in 50−74% yields with >95% regioselectivity and excellent chemoselectivity (entries 8−10). In addition, 4-methylbenzonitrile (**2b**) and 4-fluorobenzonitrile (**2c**) were also employed in the reaction, affording the corresponding products (entries 11 and 12). The reaction of an aliphatic nitrile such as octanonitrile or trimethylsilyl cyanide proved to be sluggish under these conditions.

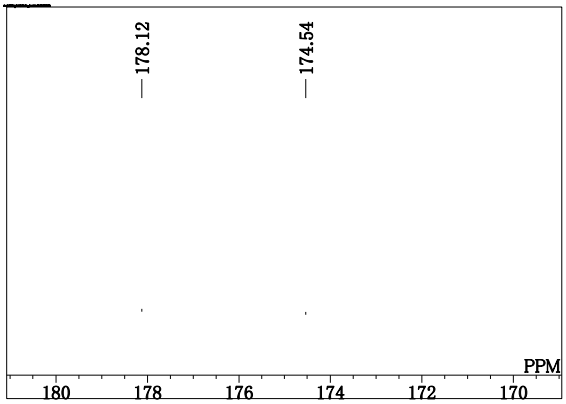
On the basis of these experiments, I propose the reaction mechanism shown in Scheme 5-5. The reaction initiates $NbCl_5$-assisted reaction of nitrile to form *N*-benzylidenebenzamidine (**A**). Subsequent cycloaddition of **A** with phenylacetylene (**1i**) on the benzylidene carbon results in the formation of 2,4,6-triphenylpyrimidine (**3i**).



Scheme 5-5. Plausible mechanism for the reaction of phnylacetylene (**1i**) and benzonitrile (**2a**)

The results in Table 5-1 show that $NbCl_5$ gives the best yields of **3a**. This is a result of differences in affinity toward the nitriles. Acetonitrile has been used as a probe molecule to observe Lewis

acidities in various IL (ionic liquids)−metal chloride pairs via FT-IR analysis.[10] I attempted to observe differences in Lewis acidities using ^{13}C-NMR spectroscopy (Scheme 5-6). The difference between the Lewis acidity of $NbCl_5$ and that of $AlCl_3$ was confirmed experimentally by adding $NbCl_5$ (0.7 mmol) to benzonitrile (1 mL). The reaction mixture was stirred at 60 °C for 10 h. In the $^{13}C\{^1H\}$-NMR spectrum of the $NbCl_5$−CN reaction mixture after the addition of benzene-d_6 at 20 °C, nitrile carbon peaks appeared at 174.7 and 178.1 ppm. However, when $AlCl_3$ was used as the Lewis acid instead of $NbCl_5$, similar peaks were not observed. Therefore, $NbCl_5$ has effectual affinity[11] toward nitriles.



Scheme 5-6. $^{13}C\{^1H\}$-NMR spectrum of the $NbCl_5$−CN

5-3. Conclusion

In summary, I have proposed a practical, general, and efficient method for the synthesis of polysubstituted pyrimidine derivatives. These synthetic methods are the first examples of transition-metal-mediated cycloaddition reactions of one alkyne molecule and two nitrile molecules to obtaine pyrimidines with excellent chemoselectivities and high regioselectivities.

5-4. Experimetal Section

General

GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. The products were characterized by ^{1}H-NMR, ^{13}C-NMR, HMQC and HMBC.

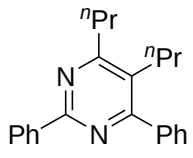
Typical Reaction Procedure for the Preparation of 3a (Entry 10, Table 5-1)

To a mixture of 4-octyne (**1a**) (110 mg, 1 mmol), benzonitrile (**2**) (2 mL), $NbCl_5$ (324mg, 1.2 mmol) was added in six batches (each 0.2 mmol), one every 2 h, and stirred for 22 h at 60°C under

Ar. The yields of products were estimated from the peak areas based on internal standard technique using GC and **3a** was obtained in 86% yield. After being quenched with 10% NaOHaq (50 mL), the organic layer was extracted with diisopropyl ether (30 mL). The solvent was evaporated under vacuum. The product **3a** was isolated by silicagel column chromatography (*n*-hexane : EtOAc = 7 : 3) in 79% yield (250 mg) as brown oil

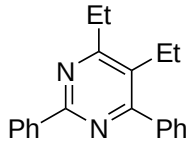
Charactarization of the compounds

2,4-Diphenyl-5,6-dipropylpyrimidine (**3a**) **:** brown oil



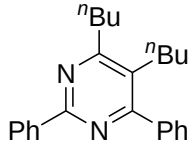
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 7.3 Hz, 3H), 1.09 (t, J = 7.3 Hz, 3H), 1.43-1.49 (m, 2H), 1.92-1.98 (m, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.86 (t, J = 8.0 Hz, 2H), 7.42-8.51 (m, 10H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 14.3 (CH_3), 21.1 (CH_2), 22.0 (CH_2), 30.3 (CH_2), 36.6 (CH_2), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.6 (C), 128.7 (CH), 130.0 (CH), 138.3 (C), 140.0 (C), 161.0 (C), 166.0 (C), 169.5 (C) ; IR (neat, cm^{-1}) 2930, 2872, 1541, 1396, 1377, 698 ; GC-MS (EI) *m/z* (relative intensity) 316 (45) $[M]^+$, 287 (100), 273 (13), 244 (2), 155 (1), 79 (3), 77 (8), 43 (1) ; HRMS (EI) *m/z* calcd for $C_{22}H_{24}N_2$ $[M]^+$ 316.1939, found 316.1928.

4,5-Diethyl-2,6-diphenylpyrimidine (**3b**) : yellow solid, mp 94-95 ^{o}C



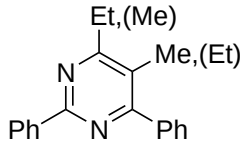
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.37 (t, J = 7.3 Hz, 3H), 2.62 (q, J = 7.2 Hz, 2H), 2.85 (q, J = 7.3, 2H), 7.35-8.43 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.8 (CH_3), 14.6 (CH_3), 21.0 (CH_2), 27.6 (CH_2), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.6 (C), 129.6 (CH), 130.0 (CH), 138.2 (C), 139.6 (C), 161.1 (C), 165.7 (C), 170.3 (C) ; IR (neat, cm^{-1}) 2972, 1539, 1394, 1024, 700 ; GC-MS (EI) *m/z* (relative intensity) 288 (35) $[M]^+$, 273 (4), 259 (4), 167 (1), 79 (1), 77 (5) ; HRMS (EI) *m/z* calcd for $C_{20}H_{20}N_2$ $[M]^+$ 288.1626, found 288.1623.

4,5-dibutyl-2,6-diphenylpyrimidine (**3c**) : brown liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.72 (t, J = 7.3 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 1.16-1.21 (m, 2H), 1.30-1.38 (m, 2H), 1.40-1.47 (m, 2H), 1.77-1.85 (m, 2H), 2.58 (t, J = 8.0 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H), 7.33-8.41 (m, 10H) ;^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 14.1 (CH_3), 22.7 (CH_2), 22.8 (CH_2), 27.5 (CH_2), 30.9 (CH_2), 32.6 (CH_2), 34.3 (CH_2), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (C), 128.6 (CH), 129.9 (CH), 138.2 (C), 139.7 (C), 161.0 (C), 165.9 (C), 169.6 (C) ; IR (neat,cm^{-1}) 2956, 1541, 1396, 1211, 691 ; GC-MS (EI) *m/z* (relative intensity) 344 (12) $[M]^+$, 301 (100), 259 (73), 224 (3), 153 (1), 79 (1), 77 (7) ; HRMS (EI) *m/z* calcd for $C_{24}H_{28}N_2$ $[M]^+$ 344.2252, found 344.2263.

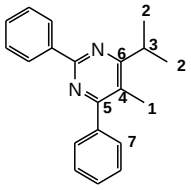
4-Ethyl-5-methyl-2,6-diphenylpyrimidine (**3e**), (5-Ethyl-4-methyl-2,6-diphenylpyrimidine (**3e'**)) : brown solid, mp 86-88 °C



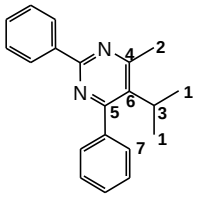
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3H), 1.18 (s, 3H), 1.34 (t, J = 7.6 Hz, 3H), 2.24 (s, 3H), 2.58 (q, J = 7.9 Hz, 2H), 2.79 (q, J = 7.5 Hz, 2H), 7.32-8.45 (m, 20H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.9 (CH_3), 14.1 (CH_3), 14.9 (CH_3), 21.6 (CH_2), 22.4 (CH_3), 28.6 (CH_2), 116.1 (CH), 123.3 (C), 128.0 (CH), 128.15 (CH), 128.2 (CH), 128.30 (CH), 128.33 (CH), 128.56 (CH), 128.59 (CH), 128.7 (CH), 129.3 (CH), 129.9 (CH), 130.0 (CH), 130.1 (C), 138.0 (C), 138.2 (C), 139.2 (C), 139.4 (C), 161.11 (C), 161.14 (C), 165.0 (C), 165.5 (C), 166.4 (C), 170.6 (C) ; IR (neat,cm^{-1}) 2961, 2938, 1541, 1395, 700 ; GC-MS (EI) m/z (relative intensity) 274 (30) [M]+, 258 (2), 245 (2), 154 (1), 91 (1), 77 (4) ; HRMS (EI) m/z calcd for $C_{19}H_{18}N_2$ [M]+ 274.1470, found 274.1473, GC-MS (EI) m/z (relative intensity) 274(48) [M]$^+$, 258 (9), 207 (5), 154 (1), 91 (2), 77 (4) ; HRMS (EI) *m/z* calcd for $C_{19}H_{18}N_2$ [M]$^+$ 274.1470, found 274.1468.

4-Isopropyl-5-methyl-2,6-diphenylpyrimidine (**3f**), (5-Isopropyl-4-methyl-2,6-diphenylpyrimidine (**3f'**) : yellow solid, mp 63-65 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 6H), 1.38 (d, J = 6.9 Hz, 6H), 2.33 (s, 3H), 2.75 (s, 3H), 3.28-3.41(m, 2H), 7.42-8.56 (m, 20H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.6 (CH_3), 21.2 (CH_3), 21.3 (CH3), 24.4 (CH_3), 28.3 (CH), 31.7 (CH), 128.0 (CH), 128.1 (2CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.2 (2CH), 129.90 (CH), 130.0 (CH), 133.6 (C), 137.8 (C), 138.0 (C), 138.4 (C), 139.5 (C), 140.4 (C), 160.6 (C), 161.0 (C), 165.4 (C), 166.1 (C), 166.2 (C), 173.9 (C) ; IR (neat,cm^{-1}) 2963, 2928, 1539, 1395, 696 ; GC-MS (EI) *m/z* (relative intensity) 288 (39) [M]+, 273 (21), 259 (19), 245 (3), 91 (2), 77 (5) ; HRMS (EI) *m/z* calcd for $C_{20}H_{20}N_2$ [M]+ 288.1626, found 288.1632, GC-MS (EI) *m/z* (relative intensity) 288 (57) [M]+, 274 (8), 258 (10), 129 (19), 79 (2), 77 (8) ; HRMS (EI) *m/z* calcd for $C_{20}H_{20}N_2$ [M]+ 288.1626, found 288.1617.

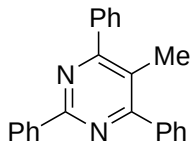


	C	Class	H	HMQC	HMBC	Correlated H
1	14.7	CH_3	2.33	2.38		
2	21.3	CH_3	1.37-1.39	1.51	1.36, 3.38	2,3
3	31.7	CH	3.28-3.41	3.30	1.36	2
4	122.5	C	×	×	2.40, 3.40	1,3
5	129.9	C	×	×	2.40, 8.53	1,7
6	133.6	C	×	×	1.36, 3.38	2,3



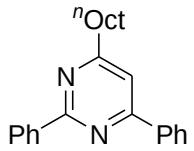
	C	Class	H	HMQC	HMBC	Correlated H
1	21.2	CH_3	1.27-1.29	1.40	1.33, 3.38	1,3
2	24.4	CH_3	2.75	2.73		
3	28.3	CH	3.28-3.41	3.28	1.35	1
4	122.5	C	×	×	3.40	3
5	129.9	C	×	×	3.37, 8.42	3,7
6	133.6	C	×	×	1.35, 2.80	1,2

5-Methyl-2,4,6-triphenylpyrimidine (**3g**) : yellow solid, mp 172-173 °C



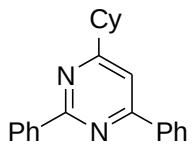
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 7.33-8.48 (m, 15H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.7 (CH_3), 123.1 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 129.0 (C), 129.2 (CH), 130.1 (CH), 137.8 (C), 139.1 (C), 161.4 (C), 166.8 (C) ; IR (neat,cm^{-1}) 3057, 2360, 1533, 1391, 692 ; GC-MS (EI) *m/z* (relative intensity) 322 (8) $[M]^+$, 216 (6), 140 (18), 115 (27), 77 (5) ; HRMS (EI) *m/z* calcd for $C_{23}H_{18}N_2$ $[M]^+$ 322.1470, found 322.1468.

4-Octyl-2,6-diphenylpyrimidine (**3h**) : brown liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 3H), 1.28-1.87 (m, 12H), 2.84 (t, J = 7.8 Hz, 2H), 7.40-7.51 (m, 7H), 8.18-8.20 (m, 2H), 8.48-8.62 (m, 2H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.9 (CH2), 29.2 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 38.2 (CH_2), 113.3 (CH), 127.2 (CH), 128.4(CH), 128.7 (CH), 128.8 (CH), 130.4 (CH), 130.5 (CH), 137.4 (C), 138.3 (C), 163.6 (C), 164.2 (C), 171.7 (C) ; IR (neat,cm^{-1}) 2955, 2855, 1572, 1373, 694 ; GC-MS (EI) *m/z* (relative intensity) 344 (2) $[M]^+$, 315 (4), 259 (14), 246 (100), 79 (3), 77 (5) ; HRMS (EI) *m/z* calcd for $C_{24}H_{28}N_2$ $[M]^+$ 344.2252, found 344.2253.

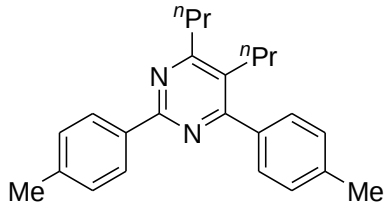
4-Cyclohexyl-2,6-diphenylpyrimidine (**3j**) : orange solid, mp 63-65 °C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25-2.07 (m, 10H), 2.75-2.81 (m, 1H), 7.43-7.51 (m, 7H), 8.19-8.21 (m, 2H), 8.61-8.63 (m, 2H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_2), 26.3 (CH_2), 32.2 (CH_2), 46.3 (CH), 111.9 (CH), 116.1 (CH), 127.2 (CH), 128.4 (CH), 128.8 (CH), 130.3 (CH), 130.5 (CH), 137.6 (C), 138.4 (C),

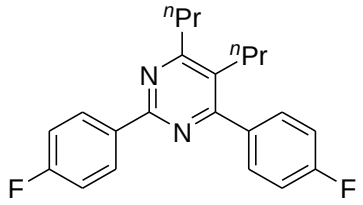
163.8 (C), 164.0 (C), 175.4 (C) ; IR (neat, cm^{-1}) 2926, 2851, 1531, 752, 684 ; GC-MS (EI) *m/z* (relative intensity) 314 (18) $[M]^+$, 259 (100), 177 (4), 135 (4), 104 (15), 77 (10) ; HRMS (EI) *m/z* calcd for $C_{22}H_{22}N_2$ $[M]^+$ 314.1783, found 314.1774.

4,5-Dipropyl-2,6-dip-tolylpyrimidine (**3k**) : colorless liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.75 (t, J = 7.3 Hz, 3H), 0.98 (t, J = 7.3 Hz, 3H), 1.34-1.41 (m, 2H), 1.81-1.88 (m, 2H), 2.27 (s, 3H), 2.31 (s, 3H), 2.54 (t, J = 8.0 Hz, 2H), 2.74 (t, J = 7.8 Hz, 2H), 7.12-8.30 (m, 8H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.2 ($2CH_3$), 21.2 (CH_3), 21.4 (CH_3), 21.9 (CH_2), 23.8 (CH_2), 30.0 (CH_2), 36.5 (CH_2), 127.9 (C), 128.0 (CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 135.6 (C), 137.0 (C), 138.2 (C), 139.8 (C), 160.9 (C), 165.8 (C), 169.2 (C) ; IR (neat, cm^{-1}) 2961, 2872, 1537, 1395, 808 ; GC-MS (EI) *m/z* (relative intensity) 344 (53) $[M^+]$, 329 (37), 315 (88), 301 (59), 143 (13), 79 (3), 77(4) ; HGMS (EI) *m/z* calcd for $C_{24}H_{28}N_2$ $[M]^+$ 344.2252, found 344.2243.

2,4-Bis(4-fluorophenyl)-5,6-dipropylpyrimidine (**3l**) : white solid, mp 68-69 ^oC



^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 1.09 (t, J = 7.6 Hz, 3H), 1.45-1.47 (m, 2H), 1.91-1.95 (m, 2H), 2.64 (t, J = 8.0 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 7.09-8.50 (m, 8H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.2 ($2CH_3$), 21.9 (CH_2), 23.8 (CH_2), 29.9 (CH_2), 36.5 (CH_2), 115.1 (CH), 115.3 (CH), 128.4 (C), 130.1 (d, J = 8.6 Hz, CH), 130.5 (d, J = 8.6 Hz, CH), 134.2 (C), 135.7 (C), 160.1 (C), 162.9 (d, J = 247 Hz, C), 164.3 (d, J = 247 Hz, C), 164.9 (CF), 165.6 (C), 169.7 (C) ; IR (neat, cm^{-1}) 2963, 2874, 1541, 1227, 848 ; (EI) *m/z* (relative intensity) 352 (8) $[M]^+$, 323 (100), 309 (3), 149 (4), 133 (24), 79 (3), 77 (2) ; HGMS (EI) *m/z* calcd for $C_{22}H_{22}N_2F_2$ $[M]^+$ 352.1751, found 352.1742.

5-5. Reference

(1) For selected reviews: (a) Lagoja, I. M. Chem. *Biodiversity* **2005,** *2*, 1. (b) Undheim, K.; Benneche, T. *In Comprehensive Heterocyclic Chemistry II;* Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Mckillop, A., Eds.; Pergamon: Oxford, UK., 1996; Vol. 6, p 93. (c) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080. (d) Hill, M. D.; Movassaghi, M. *Chem. Eur. J.* **2008**, *14*, 6836. and references therein.

(2) (a) Gompper, R.; Mair, H. –J.; Polborn, K. *Synthesis* **1997**, 696. (b) Kanbara, T.; Kushida, T.; Saito, N.; Kuwajima, I.; Kubota, K.; Yamamoto, T. *Chem. Lett.* **1992**, 583.

(3) (a) Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J. –M.; Baum, G.; Fenske, D. *Angew. Chem. Int. Ed.* **1997,** *36*, 1842. (b) Semenov, A.; Spatz, J. P.; Möller, M.; Lehn, J. –M.; Sell, B.; Schubert,

D.; Weidl, C. H.; Schubert, U. S. *Angew. Chem. Int. Ed*. **1999**, *38*, 2547.

(4) (a) Brugnatelli, G. Giorn. *Di fisica di Pavia* 1818, *1*, 117. (b)Baran, P. S.; Shenvi, R. A.; Nguyen, S. A. *Heterocycles*. **2006**, *70*, 581. (c) Ahmad, O. M.; Hill, M. D.; Movassaghi, M.; *J. Org. Chem*. **2009**. *74*, 8460. (d) Molteni, V.; Hamilton, M.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. *Synthesis* **2002**, 1669. (e) Martinez, A. G.; Fernández, A. H.; Jiménez.; Frail, A. G.; Subramanian, L. R.; Hanack, M. *J. Org. Chem*. **1992**, *57*, 1627. (f) Kakiya, H.; Yagi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc*. **2002**, *124*, 9032. (g) Pourzal, A. –A. *Synthesis* **1983**, 717. (h) Garcia, M. A.; Herrera, F. A.; Martines, A. R.; Silva, L. M. C.; Molero, V. D.; Subramanian, L. R.; Hanack, M, *Synthesis* **1990**, 881. (i) Angerer, S. von, *Scienece of Synthesis* **2004**, *16*, 379.

(5) Recent reports on the formation of pyrimidine derivatives by transition metals: (a) Lin, M.; Chen, Q. -Z.; Zhu, Y.; Chen, X. -L.; Cai, J. -J.; Pan, Y. -M.; Zhan, Z. -P. *Synlett*. **2011**, 1179. (b) Sasada, T.; Aoki, Y.; Ikeda, R.; Sakai, N.; Konakahara, T. *Chem. Eur. J*. **2011**, *17*, 9385. (c) Sasada, T.; Kobayashi, F.; Sakai, N.; Konakahara, T. *Org. Lett*. **2009**, *11*, 2161. (d) Alacid, E.; Nájera, C. *Org, Lett*. **2008,** *10*, 5011.

(6) Transition-metal-catalyzed [2+2+2] cycloaddition to form pyridines: (a) Volhardt, K. P. C. *Angew. Chem.* **1984**, *96*, 525; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539. (b) Bönnemann, H. *Angew. Chem.* **1985**, *97*, 264; *Angew. Chem. Int. Ed.* **1985**, *24*, 248. (c) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (d) Chopade, P. R.; Louie, J. *Adv. Synth. Catal*. **2006**, *348*, 2307. (e) Heller, B.; Hapke, M. *Chem. Soc. Rev*. **2007**, *36*, 1085. (f) Varela, J. A.; Saá, C. *Synlett*. **2008**, 2571. (g) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc*. **2002**, *124*, 5059. (h) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **2002**, *124*, 3518. (i) Domínguez, G.; Pérez-Castells, J, *Chem. Soc. Rev*. **2011**, *40*, 3430.

(7) (a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc*. **1987**, *109*, 6551. (b) Hartung, J, B.; Pedersen, S, F. *J. Am. Chem. Soc*. **1989**, *111*, 5468. (c) Roskamp, E, J.; Dragovich, P, S.; Hartung, J, B.; Pedersen, S, F. *J. Org. Chem*. **1989**, *54*, 4736. (d) Hartung, J, B.; Pedersen, S, F. *Organometallics***.** **1990**, *9*, 1414. (e) Obora, Y.; Kimura, M.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2005**, *901*. (f) Obora, Y.; Kimura, M.; Ohtake, T.; Tokunaga, M.; Tsuji, Y. *Organometallics* **2006**, *25*, 2097.

(8) (a) Obora, Y.; Takeshita, K.; Ishii, Y. *Org. Biomol. Chem*. **2009**, *7*, 428. (b) Obora, Y.; Satoh, Y.; Ishii, Y. *J. Org. Chem.* **2010**, *75*, 6046. (c) Satoh, Y.; Obora, Y. *Org. Lett*. **2011**, *13*, 2568. (d) Satoh, Y.; Obora, Y. *J. Org. Chem*. **2011**, *76*, 8569.

(9) (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem*. **1992**, *57*, 1973. (b) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett*. **1990**, *31*, 365. (c) Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, T. *Tetrahedron Lett*. **1990**, *31*, 369. (d) Fürstner, A.; Hupperts, A.; Ptock A.; Janssen, E. *J*. Org. Chem. **1994**, *59*, 5215. (e) Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron*. **1992,** *48*, 3867. (f) Oshiki, T.; Nomoto, H.; Tanaka, K.;Takai, K. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 1009. (g) Du, J, A, K.; Viljoen, J, S.; Du Toit, C, J. *J. Mol. Cat.* **1991**, *64*, 269. (h) Kakeya,

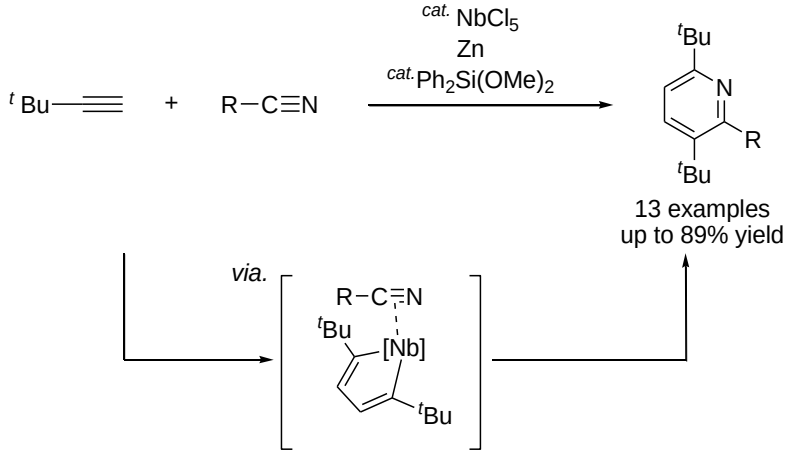
M.; Fujihara, T.; Kasaya, T.; Nagasawa, A. *Organometallics*, **2006**, *25*, 4131.

(10) (a) Mittal, N.; Nisola, G. M.; Chung, W. –J. *Tetrahedron Lett.* **2012**, doi: 10.1016/j.tetlet.2012.04.045. (b)Yang, Y. –L.; Kou, Y. *Chem. Commun*. **2004**, 226. (c) Platero, E. E.; Mentruit, M. P.; Morterra, C. *Langmuir* **1999**, *15*, 5079.

(11) (a) Marchetti, F.; Pampaloni, G. *Chem. Commun*. **2012**, 48, 635. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J*. **2000**, *6*, 3491.

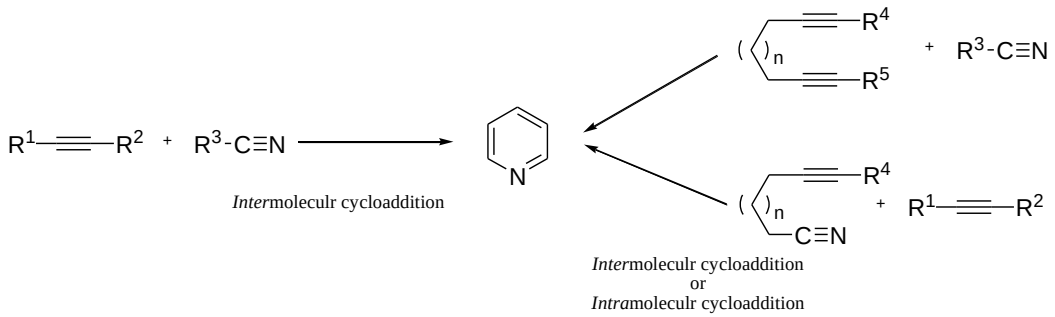
Chapter 6

Low-Valent Niobium-Catalyzed Intermolecular [2+2+2] Cycloaddition of *tert*-Butylacetylene and Arylnitriles to Form 2,3,6-Trisubstituted Pyridine Derivatives



6-1. Introduction

Pyridine derivatives are an important class of azaheterocyclic compounds and including natural products, biologically active substances,[1] functional materials[2] and ligands.[3] By way of example, niacin and vitamin B_6 are both well-known pyridine derivatives. Neutral pyridine-based pillaring ligands are also employed in the construction of metal−organic frameworks (MOFs), since they can be fully exchanged with different pyridine-based ligands to enable "stepwise" MOF synthesis.[4] Among the methods available for the synthesis of pyridines, the transition-metal-catalyzed cycloaddition reaction of alkynes with nitriles is of particular importance, since this methodology is capable of introducing various substituent groups onto the pyridine ring (scheme 6-1).[5–11] Many of the reported cycloaddition reactions have been intramolecular reactions using α,ω-diynes or cyanoalkynes. For instance, Takeuchi and co-workers reported that pyridines could be formed from the Ir-catalyzed [2 + 2 + 2] cycloaddition of α,ω-diynes with nitriles.[8]



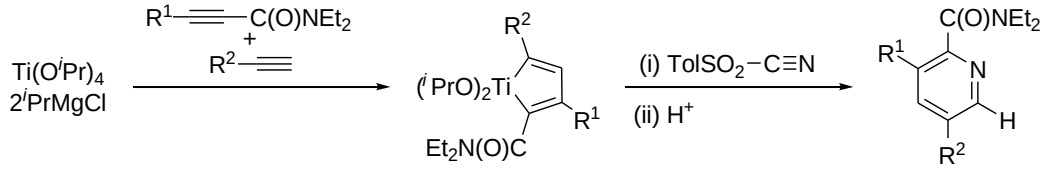
Scheme 6-1. Transition-metal mediated cycloaddition of alkynes with nitriles to pyridines

Alternatively, the transition-metal-catalyzed intermolecular [2 + 2 + 2] cross-cycloaddition reaction between two alkyne molecules and one nitrile is one of the simplest and most atom economical methods for preparing pyridines. However, little work has been reported in this field because of the difficulty in controlling the chemo- and regioselectivity of the reaction. Wakatsuki and Yamazaki reported that a Co-catalyzed reaction was the first example of the synthesis of pyridines via the [2 + 2 + 2] intermolecular cycloaddition reactions of alkynes with nitriles.[6a] These intra- and intermolecular cycloaddition reactions typically employ late transition metals as catalysts, such as Co,[6] Rh,[7] Ir,[8] Ni,[9] Ru[10] and Fe.[11]

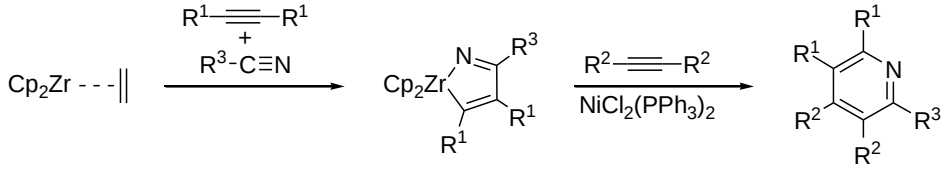
The synthesis of pyridines in this manner has not yet been achieved using early transition metals as catalysts. Some stoichiometric reactions employing early transition metals have, however, been reported (Scheme 6-2), such as the synthesis of pyridines from two alkynes, a nitrile and $Ti(O^iPr)_2$,[12] the Zr/Ni-mediated cyclotrimerization of alkynes and nitriles to give pentasubstituted pyridines[13] and the preparation of tetrasubstituted pyridines from the reaction of Ta-alkyne complexes with alkynenitriles.[14] In addition, My research group has reported the $NbCl_5$-mediated intermolecular

cycloaddition reaction of alkynes with benzonitriles.[15] This reaction did not produce pyridines, though, and instead gave pyrimidines when using a stoichiometric amount of $NbCl_5$ (Scheme 6-3, "Previous work").

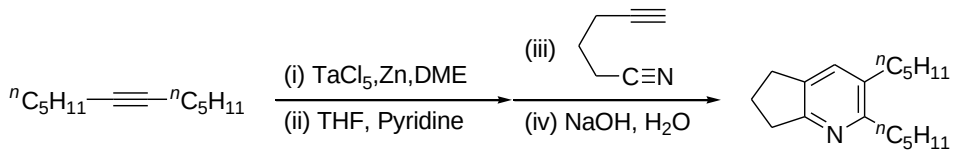
Sato (ref.12)



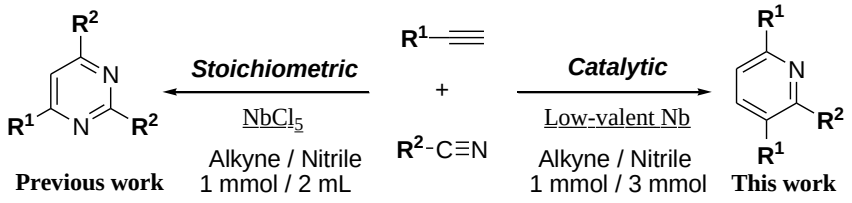
Takahashi (ref.13)



Takai (ref.14)



Scheme 6-2. Stoichiometric reaction of alkynes with nitriles to pyridines

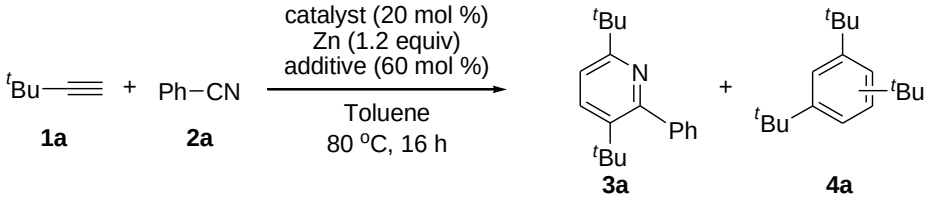


Scheme 6-3. Transition-metal-catalyzed [2+2+2] cycloaddition of alkynes with nitriles

Recently, My group reported that the $NbCl_3(DME)$[16] is a useful catalyst for the selective synthesis of 1,3-cyclohexadienes from the reaction of alkynes with alkenes.[17] I additionally determined that the $NbCl_5$/hydrosilane system serves as an efficient low-valent Nb catalyst for the selective cycloaddition of alkynes and alkenes to form 1,3-cyclohexadienes.[17c]

6-2. Result and Discussion

Table 6-1. $NbCl_5$/Zn/$Ph_2Si(OMe)_2$ Catalyzed Reaction of *tert*-Butylacetylene (1a) with Benzonitrile (2a) under Various Conditions[a]



Entry	Catalyst	Additive	Yield (%)[b] 3a	Yield (%)[b] 4a
1[c]	$NbCl_3$(DME)	none	11(95)	36
2[c]	$NbCl_5$	none	n.d.[g]	n.d.[g]
3	$NbCl_5$	none	26(77)	41
4	$NbCl_5$	$PhSiMe_3$	33(88)	43
5	$NbCl_5$	$PhSi(OMe)_3$	70(97)	17
6	$NbCl_5$	$MeSi(OMe)_3$	72(98)	18
7	$NbCl_5$	$Ph_2Si(OMe)_2$	82[74[(98)	10
8[d]	$NbCl_5$	$Ph_2Si(OMe)_2$	64(98)	27
9[e]	$NbCl_5$	$Ph_2Si(OMe)_2$	38(96)	15
10[f]	$NbCl_5$	$Ph_2Si(OMe)_2$	27(96)	7
11	$NbCl_3$(DME)	$Ph_2Si(OMe)_2$	47(71)	15
12	$TaCl_5$	$Ph_2Si(OMe)_2$	trace	8
13	$ZrCl_4$	$Ph_2Si(OMe)_2$	n.d.[g]	n.d.[g]

(a) Reaction conditions: **1a** (1 mmol), **2a** (3 mmol), catalyst (0.2 mmol), Zn (1.2 mmol) and additive (0.6 mmol) in toluene (2 mL) at 80 °C for 16 h under Ar. (b) Yields were determined by GC on the basis of the quantity of **1a** used. All are GC yields except the value in the square brackets. The numbers in parentheses show the selectivity (%) of the 2,3,6-substituted adduct of **3a**. (c) Without Zn. (d) **1a** (1 mmol) and **2a** (0.5 mmol) were used. (e) Zn (0.2 mmol) was used. (f) $NbCl_5$ (0.1 mmol), Zn (1.1 mmol), $Ph_2Si(OMe)_2$ (0.3 mmol) were used. (g) Not detected by GC.

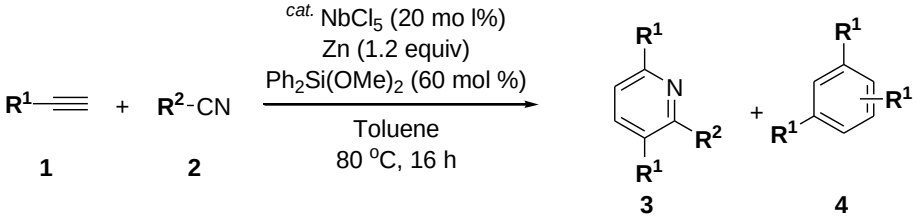
Initially, *tert*-butylacetylene (**1a**) and benzonitrile (**2a**) were used as model substrates for the optimization of the cycloaddition reaction conditions, with the results presented in Table 6-1. I investigated various low-valent niobium species. When **1a** (1 mmol) was reacted with **2a** (3 mmol) in the presence of $NbCl_3$(DME) (0.2 mmol) in toluene (2 mL) at 80 °C for 16 h, the reaction produced trisubstituted pyridine (**3a**) in 11% yield as well as **4a** in 36% yield (entry 1). Previously, I

reported that $NbCl_5$ is an effective agent for the activation of nitriles.[15] I therefore applied $NbCl_5$ to this reaction; however, the result was that neither **3a** nor **4a**[18] were observed in the products (entry 2). When low-valent Nb species were instead generated by $NbCl_5$ in conjunction with Zn,[19] **3a** was given in 26% yield with good regioselectivity (entry 3). The data related to subsequent screening of silane compounds as additives are shown in entries 4−7 and reveal that alkoxysilanes are effective for this reaction. Between the two alkoxysilanes tested, $Ph_2Si(OMe)_2$ demonstrated the most pronounced influence on reactivity, producing **3a** in the best yield with excellent regioselectivity. However, other additives ($AgSbF_6$, 1,1-bis(diphenyldiphosphino)methane), and biacetyl-bis-(phenylimine)) exhibited no activity in the formation of pyridine derivatives. On the basis of the results of these experiments, the presence of alkoxy substituents on the silyl group is useful for the cycloaddition of alkynes and nitriles (entry 4 vs entry 5). Interestingly, even when **1a** and **2a** were allowed to react in a stoichiometric molar ratio (**1a**:**2a** = 2:1), the yield of the product was still acceptable at 64% (entry 8). As the catalyst precursor for this reaction, the Nb(V) complex $NbCl_5$ appears to be highly efficient. While $NbCl_3$(DME) was used as catalyst under these conditions, **3a** was obtained in moderate yield (entry 11). When early transtion-metal analogues, $TaCl_5$ and $ZrCl_4$, were used as the catalyst, even though **1a** was evidently converted during the course of the reaction, almost none of the desired pyridine was observed (entries 12 and 13).

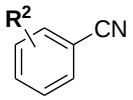
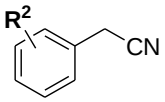
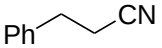
Using the optimized conditions shown in Table 6-1, entry 7, the reactions of various nitriles (**2**) were examined (Table 6-2). **1a** was reacted with various benzonitriles with substituents on the benzene ring (**2a**−**2g**) under the optimized conditions (entries 1−7). The benzonitrile derivatives 4-tolunitrile (**2b**), 4-chlorobenzonitrile (**2c**), 4-(trifluoromethyl)benzonitrile (**2d**), 4-cyanobenzoate (**2e**) and 3-tolunitrile (**2f**) participated in the reaction, and the corresponding 2,3,6-trisubstituted pyridines (**3b**−**3f**) were obtained in 51−82% yields with high chemoselectivities and excellent regioselectivities. When 2-tolunitrile (**2g**) was applied to this reaction, the desired pyridines (**3g**) were obtained in 48% yield with excellent regioselectivity, although substituted benzenes from the cyclotrimerization of **1a** were also obtained in 23% yield.

I next investigated the scope of the reaction using various benzylnitriles (entries 8−12). Phenylacetonitrile (**2h**) and its derivatives 4-methylphenylacetonitrile (**2i**), 4-chlorophenylacetonitrile (**2j**), 4-methoxyphenylacetonitrile (**2k**) and 3,4-dichlorophenylacetonitrile (**2l**) all underwent reaction, and the corresponding pyridines (**3h**−**3l**) were obtained in 66−89% yields. The reaction of 3-phenylpropanenitrile (**2m**) with **1a** afforded the corresponding 2,3,6-trisubstituted pyridine in 71% yield with 98% regioselectivity (entry 13). The reaction was sluggish with aliphatic nitriles such as octanenitrile, trimethylsilyl cyanide, and ethyl cyanoformate and did not produce desired pyridines under these conditions. The use of *tert*-butylacetylene (**1a**) was a suitable substrate in the present reaction. However, when triethylsilylacetylene (**1b**) was used in the reaction, it underwent conversion to a moderate extent, and a negligible amount of the

Table 6-2. $NbCl_5$/Zn/$Ph_2Si(OMe)_2$ Catalyzed Reactions of Acetylenes (1) and Nitriles (2) Leading to 2,3,6-Trisubstituted Pyridines[a]

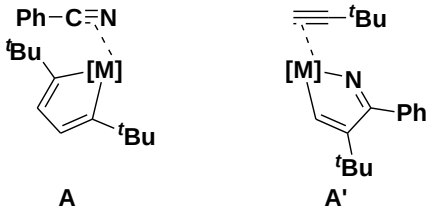


1 **2** **3** **4**

Entry	**1**(R^1)	**2**(R^2)	Yield (%) **3**[b]	Yield (%) **4**[c]
				
1	^{t}Bu (**1a**)	H (**2a**)	74 (**3a**)	10 (**4a**)
2	(**1a**)	4-Me (**2b**)	74 (**3b**)	15 (**4a**)
3	(**1a**)	4-Cl (**2c**)	82 (**3c**)	15 (**4a**)
4	(**1a**)	4-CF_3 (**2d**)	51 (**3d**)	11 (**4a**)
5	(**1a**)	4-CO_2Me (**2e**)	53 (**3e**)	11 (**4a**)
6	(**1a**)	3-Me (**2f**)	71 (**3f**)	12 (**4a**)
7	(**1a**)	2-Me (**2g**)	48 (**3g**)	23 (**4a**)
				
8	(**1a**)	H (**2h**)	87 (**3h**)	8 (**4a**)
9	(**1a**)	4-Me (**2i**)	85 (**3i**)	7 (**4a**)
10	(**1a**)	4-Cl (**2j**)	89 (**3j**)	8 (**4a**)
11	(**1a**)	4-OMe (**2k**)	66 (**3k**)	trace
12	(**1a**)	3,4-dichloro (**2l**)	75 (**3l**)	15 (**4a**)
13	(**1a**)	 (**2m**)	71 (**3m**)	9 (**4a**)
14	TES[d] (**1b**)	(**2a**)	trace	trace
15	Ph (**1c**)	(**2a**)	trace	39 (**4b**)

(a) Reaction conditions: See optimized conditions (Table 6-1, entry 7). (b) 2,3,6-Trisubstituted pyridines were all obtained with >96% regioselectivity. (c)Yields were determined by GC on the basis of the quantity of **1** used. (d) TES = triethylsilyl.

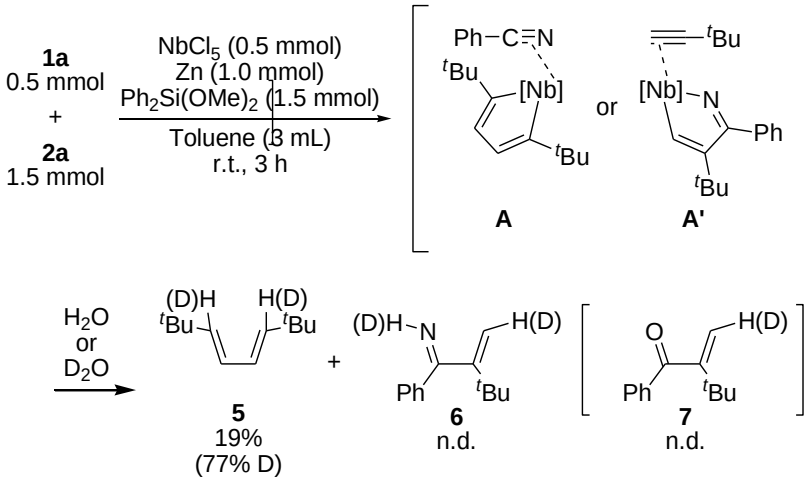
formation of the desired pyridine was detected (entry 14). The reaction with methyl propiolate did not give any corresponding product. The reaction of certain terminal alkynes with **2a** was observed to preferentially result in cyclotrimerization of the alkyne rather than cross-cyclotrimerization of the alkyne and nitrile. As an example, when phenylacetylene (**1c**) was used in the reaction, trace amount of the desired pyridine derivative was detected, whereas **4c** was obtained in 39% yield (entry 15). In case of the reaction of dynes or internal alkynes with **2a**, alkynes were converted, but any products were not obtained.



Scheme 6-4. Transition-metal intermediate in the reaction of **1a** with **2a**

In general, the results detailed above are notable since they demonstrate the preparation of pyridine derivatives via reactions involving catalysis by a low-valent early transition metal.

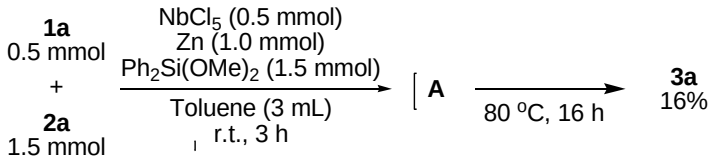
The synthesis of pyridines via the transition-metal-catalyzed cycloaddition reactions of alkynes with nitriles, as demonstrated in this work, may proceed via two possible transition metal intermediates (Scheme 6-4).[20]



Scheme 6-5. Examination of the formation of niobacyclic intermediates

These two intermediates are shown in Scheme 6-4. Depending on the path, the key intermediate in the reaction is either niobacyclopentadiene (**A**) or aza-niobacyclopentadiene (**A′**). To determine

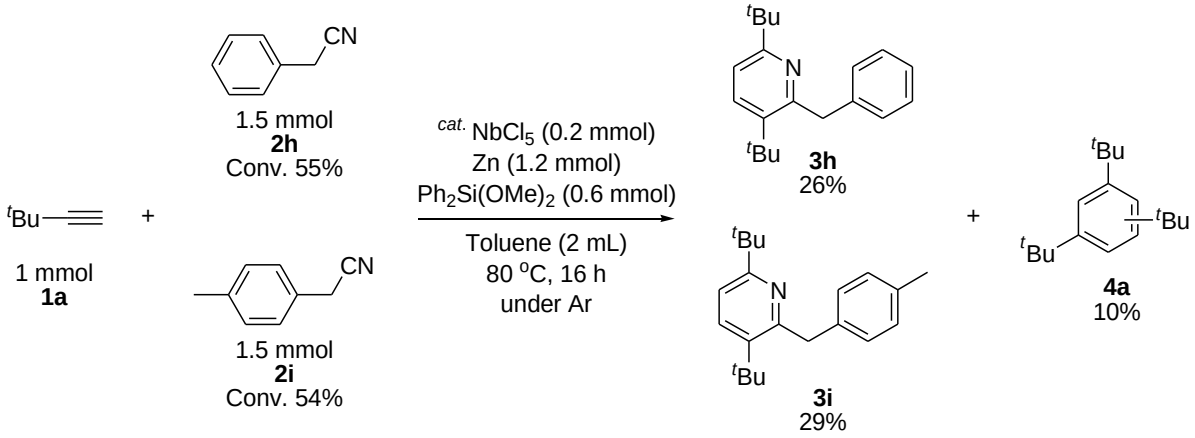
which of these two intermediates is the most plausible, I carried out experiments to evaluate the formation of either compound (Scheme 6-5). I first examined the stoichiometric reaction of **1a** with **2a** under optimized condition (Scheme 6-5). The reaction mixture was stirred at room temperature for 3 h, after which it was quenched with either H_2O or D_2O to hydrolyze or deuteriolyze whichever key intermediate had formed (**A** or **A′**). The results of GC analysis of the products showed that the diene (**5**) derived from the niobacyclopentadiene complex (**A**)[18] was obtained in 19% (77% D incorporated after deuteriolysis) yield, while the aza-diene (**6**) or hydrolysis product (**7**) derived from **A′** was not observed.



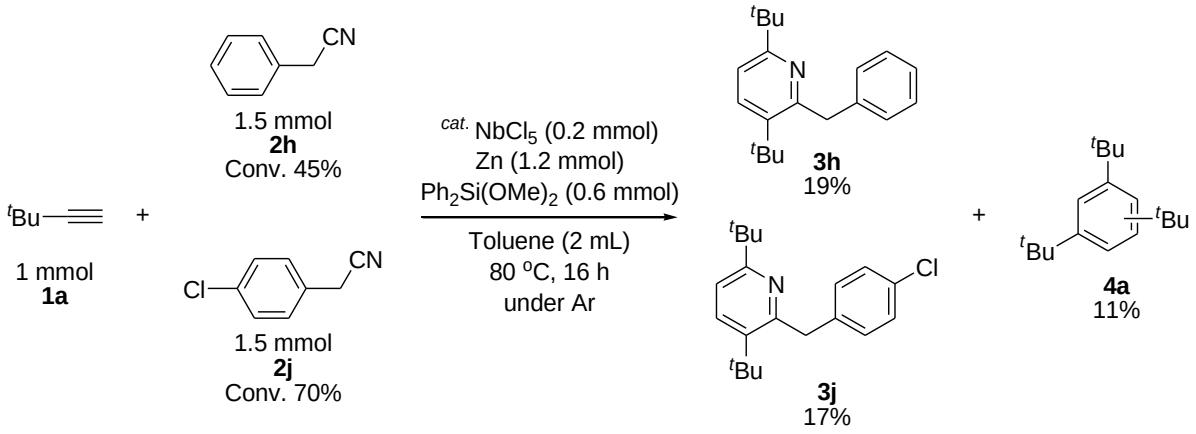
Scheme 6-6. Reaction of **1a** and **2a** via the formation of **A**

After the in situ formation of this niobacyclopentadiene complex, the reaction mixture was stirred at 80 °C for 16 h (i.e., standard conditions), and the corresponding pyridine derivative (**3a**) was obtained in 16% yield (Scheme 6-6).

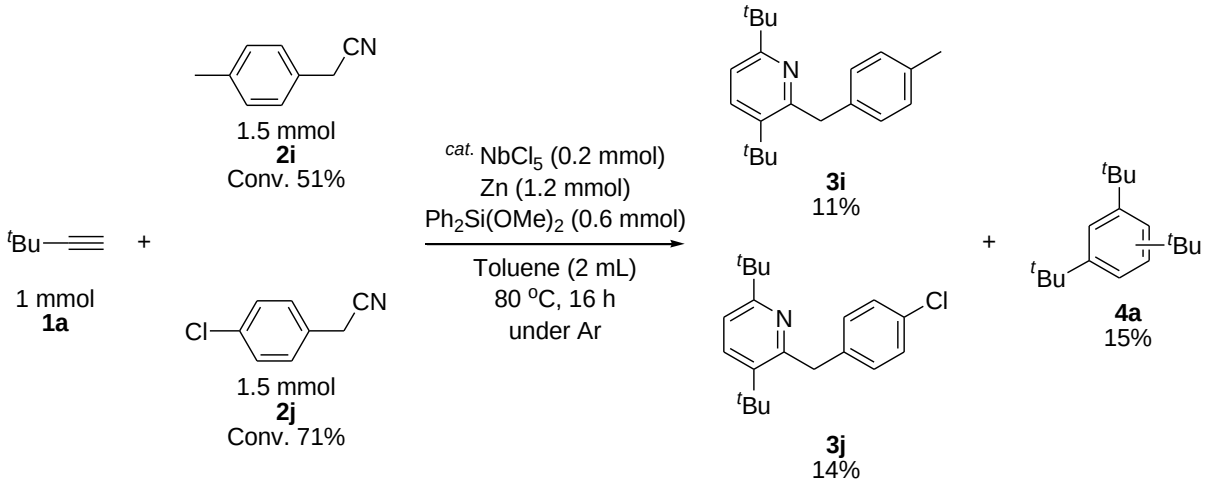
Furthermore, to get more insights of reaction mechanism, I performed intermolecular competition experiments between differently substituted phenylacetoniriles (Scheme 6-7, 6-8, and 6-9). On the basis of these competition experiments, substantial electronic effect on aryl ring relevant to the coordination of Nb center was not observed.



Scheme 6-7. Reaction of **1a**, **2h**, and **2i** under the optimized condition

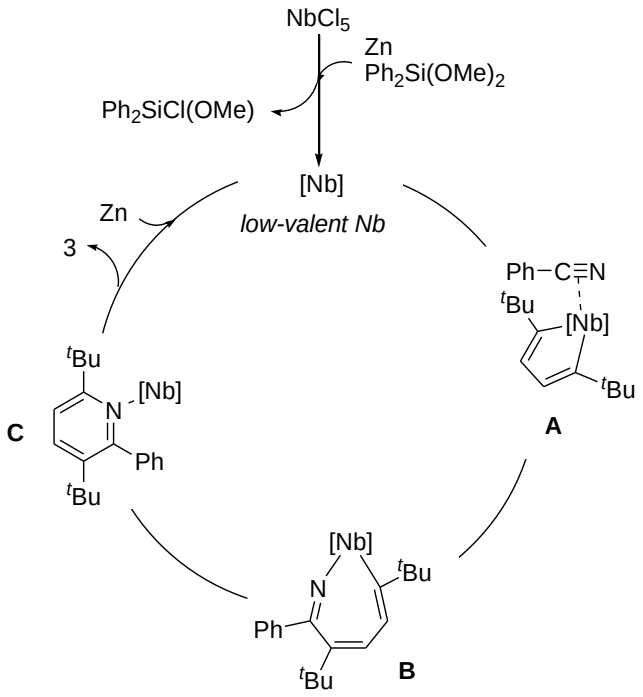


Scheme 6-8. Reaction of **1a**, **2h**, and **2j** under the optimized condition



Scheme 6-9. Reaction of **1a**, **2i**, and **2j** under the optimized condition

On the basis of these results, my proposed reaction mechanism is shown in Scheme 6-10. In this reaction pathway, the initial step is the generation of the low-valent Nb species from $NbCl_5$, in which Zn[19] acts as a reducing agent. It should be noted that this active low-valent Nb species might also be stabilized by the alkoxysilane, and generated chloro(methoxy)diphenylsilane.[21] Subsequently, the oxidative cycloaddition of two alkyne molecules to low-valent [Nb] takes place and forms the niobacyclopentadiene intermediate (**A**).[18] Migratory insertion of the nitrile into **A** produces the aza-niobaheptatriene intermediate (**B**), and **B** forms the corresponding pyridine derivative (**3**) via **C.** All attempts to isolate or fully characterize the 5-membered niobacyclic intermediates (**A**) and their corresponding 7-membered niobacyclic intermediates (**B**) have been unsuccessful because of the unstability of these niobium species.



Scheme 6-10. A plausible reaction mechanism

6-3. Conclusion

In summary, I have developed a low-valent niobium catalyzed [2 + 2 + 2] intermolecular cycloaddition reaction between terminal alkynes and nitriles to produce 2,3,6-trisubstituted pyridine derivatives. This catalytic system is the first example of the synthesis of pyridines from the reaction of alkynes with nitriles using an early transition metal.

6-4. Experimental Section

General Methods

GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. The products were characterized by ^{1}H NMR, ^{13}C NMR, HMQC and HMBC.

Typical Reaction Procedure for the Preparation of 3a (Entry 7, Table 6-1)

A mixture of *tert*-butylacetylene (**1a**) (82 mg, 1 mmol), benzonitrile (**2a**) (309 mg, 3 mmol), $NbCl_5$ (54 mg, 0.2 mmol), Zn (78 mg, 1.2 mmol), $Ph_2Si(OMe)_2$ (146 mg, 0.6 mmol) and toluene (2 mL) was stirred for 16 h at 80 °C under Ar. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **3a** was obtained in 82% yield.

The products 3a were isolated by silica gel column chromatography (*n*-hexane:EtOAc = 100:0 to 50:1 as eluent) in 74% yield 99 mg) as yellow liquid.

Typical Reaction Procedure for the Preparation of 5 (Scheme 6-5)

A mixture of *tert*-butylacetylene (**1a**) (49 mg, 0.5 mmol), benzonitrile (**2a**) (154 mg, 1.5 mmol), $NbCl_5$ (135 mg, 0.5 mmol), Zn (65 mg, 1.0 mmol), $Ph_2Si(OMe)_2$ (365 mg, 1.5 mmol) and toluene (3 mL) was stirred for 3 h at room tempreture under Ar. Thereafter, the formation of Nb-cyclopentadiene complex (**A**) was verified by hydrolysis or deuteriolysis of the reaction mixture affording **5**. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **5** was obtained in 19% yield.

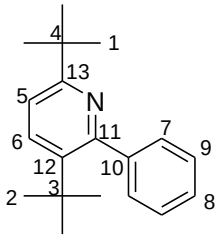
Typical Reaction Procedure for the Preparation of 3a (Scheme 6-6)

A mixture of *tert*-butylacetylene (**1a**) (49 mg, 0.5 mmol), benzonitrile (**2a**) (154 mg, 1.5 mmol), $NbCl_5$ (135 mg, 0.5 mmol), Zn (65 mg, 1.0 mmol), $Ph_2Si(OMe)_2$ (365 mg, 1.5 mmol) and toluene (3 mL) was stirred for 3 h at room tempreture under Ar. Subsequently, the reaction mixture was stirred at 80 °C for 16 h. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **3a** was obtained in 16% yield.

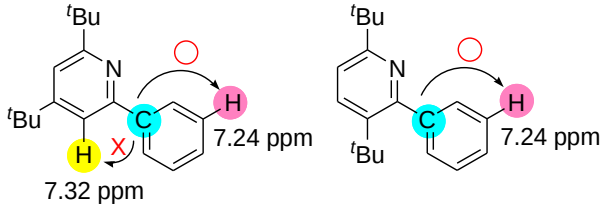
Characterization of the compounds

3,6-Di-*tert*-butyl-2-phenylpyridine (**3a**): yellow liquid

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.43 (s, 9H), 7.27−8.09 (m, 7H); ^{13}C- NMR (100 MHz, $CDCl_3$) δ 30.4 (CH_3), 30.8 (CH_3), 35.0 (C), 37.8 (C), 114.2 (CH), 114.24 (CH), 127.0 (2CH), 128.4 (2CH), 128.5 (CH), 140.6 (C), 155.4 (C), 160.4 (C), 168.8 (C); IR (neat, cm^{-1}) 2962, 2868, 1597, 1301; GC−MS (EI) m/z (relative intensity) 267 (62) [M^+], 252 (100), 211 (19), 154 (2), 79 (1), 77 (4), 57(57); HRMS (EI) m/z calcd for $C_{19}H_{25}N$ [M]$^+$ 267.1987, found 267.1975.

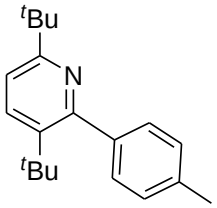


	C	Class	H	HMQC	HMBC	Correlated H
1	30.4	***C***H_3	1.43	1.81	1.43	**1**
2	30.8	***C***H_3	1.36	1.76	1.51	**2**
3	35.0	***C***			1.44	**2**
4	37.8	***C***			1.51	**1**
5	114.2	***C***H	7.24	7.14	7.53	**6**
6	114.3	***C***H	7.27	7.32	7.26	**5**
7	127.0	***C***H	8.09	7.90	7.34	**8**
8	128.4	***C***H	7.24-8.09	7.24	8.06	**7**
9	128.5	***C***H	7.24-8.09	7.24	7.45	**9**
10	140.6	***C***			7.24	**9**
11	155.4	***C***			8.06	**7**
12	160.4	***C***			1.44	**2**
13	168.8	***C***			1,52	**1**



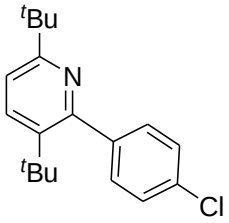
Observed by HMBC

3,6-Di-*tert*-butyl-2-*p*-tolylpyridine (**3b**): yellow liquid



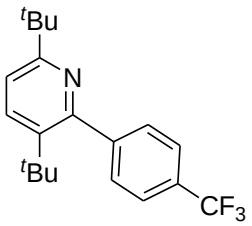
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.34 (s, 9H), 2.29 (s, 3H), 7.10−7.89 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 30.4 (CH_3), 30.8 (CH_3), 34.9 (C), 37.8 (C), 113.9 (CH), 114.0 (CH), 126.9 (2CH), 129.2 (2CH), 137.8 (C), 138.2 (C), 155.5 (C), 160.3 (C), 168.7 (C); IR (neat, cm^{-1}) 2962, 2868, 1597, 1477, 1394; GC−MS (EI) m/z(relative intensity) 281 (61) [M^+], 266 (100), 225 (20), 191 (1), 167 (2), 91 (4), 77 (2), 57(2); HRMS (EI) m/z calcd for $C_{20}H_{27}N$ $[M]^+$ 281.2144, found 281.2137.

3,6-Di-*tert*-butyl-2-(4-chlorophenyl)pyridine (**3c**): yellow liquid



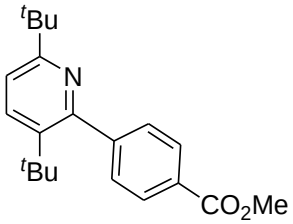
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.01 (s, 9H), 6.84−7.62 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.4 (CH_3), 30.8 (CH_3), 35.0 (C), 37.8(C), 114.0 (CH), 114.5 (CH), 128.2 (2CH), 128.6 (2CH), 134.4 (C), 139.0 (C), 154.2 (C), 160.7 (C), 169.0 (C); IR (neat, cm^{-1}) 2976, 2872, 1598, 1496; GC−MS (EI) m/z (relative intensity) 301 (54) [M^+], 286 (100), 245 (18), 111 (1), 77 (3), 57(4); HRMS (EI) m/z calcd for $C_{19}H_{24}ClN$ $[M]^+$ 301.1597, found 301.1593.

3,6-Di-*tert*-butyl-2-(4-(trifluoromethyl)phenyl)pyridine (**3d**): yellow liquid



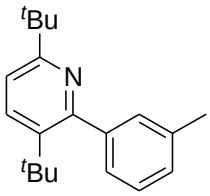
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.34 (s, 9H), 7.25−8.11 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.8 (CH_3), 35.0 (C), 37.8 (C), 114.6 (CH), 116.1 (CH), 124.0 (C), 125.42 (2CH), 127.2 (2CH), 130.2 (C), 143.9 (C), 154.0 (C), 160.9 (C), 169.2 (C); ^{19}F-NMR (400 MHz, $CDCl_3$) δ = −62.4 (s, CF_3); IR (neat, cm^{-1})2968, 2872, 1620, 1411; GC−MS (EI) m/z (relative intensity) 335 (48) [M^+], 334 (47), 320 (100), 305 (12), 279 (14), 222 (1), 77 (1), 57 (3); HRMS (EI) m/z calcd for $C_{20}H_{24}F_3N$ $[M]^+$ 335.1861, found 335.1868.

Methyl 4-(3,6-di-*tert*-butylpyridin-2-yl)benzoate (**3e**): yellow liquid



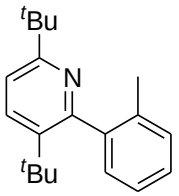
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.32 (s, 9H), 3.8 (s, 3H), 7.21 (s, 1H), 7.49 (s, 1H), 8.07 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.8 (CH_3), 34.9 (C), 37.7 (C), 114.7 (CH), 114.9 (CH), 126.7 (2CH), 129.7 (C), 129.8 (2CH), 144.6(C), 154.1 (C), 160.6 (C), 166.9 (C), 169.0 (C); IR (neat, cm^{-1}) 2978, 2870, 1730, 1394, 1112; GC−MS (EI) m/z (relative intensity) 325 (52) [M^+], 310 (100), 269 (18), 267(3), 190 (5), 79(1), 77 (2), 57 (3); HRMS (EI) m/z calcd for $C_{21}H_{27}NO_2$ $[M]^+$ 325.2042, found 325.2029.

3,6-Di-*tert*-butyl-2-*m*-tolylpyridine (**3f**): yellow liquid



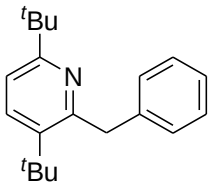
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.34 (s, 9H), 2.33 (s, 3H), 7.07−7.77 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 30.4 (CH_3), 30.8 (CH_3), 34.9 (C), 37.8 (C), 114.0 (CH), 114.4 (CH), 124.2 (CH), 127.7 (CH), 128.4 (CH), 129.1 (CH), 138.0 (C), 140.6 (C), 155.7 (C), 160.3 (C), 168.7 (C); IR (neat, cm^{-1}) 2963, 2868, 1597, 1249; GC− MS (EI) m/z (relative intensity) 281 (64) [M^+], 266 (100), 225 (17), 210 (6), 169 (1), 91 (4), 77 (1), 57(1); HRMS (EI) m/z calcd for $C_{20}H_{27}N$ [M]$^+$ 281.2144, found 281.2137.

3,6-Di-*tert*-butyl-2-*o*-tolylpyridine (**3g**): yellow liquid



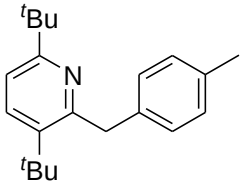
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.32 (s, 9H), 2.35 (s, 3H), 7.12−7.37 (m, 6H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 20.8 (CH_3), 30.4 (CH_3), 30.8 (CH_3), 34.9 (C), 37.8 (C), 113.3 (CH), 118.1 (CH), 125.7 (CH), 127.8 (CH), 129.8 (CH), 130.9 (CH), 136.4 (C), 141.5 (C), 158.4 (C), 159.9 (C), 168.2 (C); IR (neat, cm^{-1}) 2964, 2904, 1701, 1595, 1404; GC−MS (EI) m/z (relative intensity) 281 (92) [M^+], 266 (99), 225 (18), 210 (5), 169 (2), 91 (6), 77 (2), 57(3); HRMS (EI) m/z calcd for $C_{20}H_{27}N$ [M]$^+$ 281.2143, found 281.2137.

3,6-Di-*tert*-butyl-2-benzylpyridin (**3h**): yellow liquid;



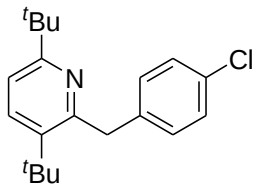
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.36 (s, 9H), 4.10 (s, 2H), 6.88−7.33 (m, 7H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 37.5 (C), 45.0 (CH_2), 113.0 (CH), 116.7 (CH), 125.9 (2CH), 128.2 (2CH), 129.1 (CH), 140.5(C), 159.0 (C), 160.1 (C), 168.5 (C); IR (neat, cm^{-1}) 2965, 2868, 1685, 1598, 1558; GC−MS (EI) m/z (relative intensity) 281 (80) [M^+], 266 (100), 225 (19), 168 (2), 91 (11), 79 (2), 77 (3), 57(2); HRMS (EI) m/z calcd for $C_{20}H_{27}N$ [M]$^+$ 281.2144, found 281.2144.

3,6-Di-*tert*-butyl-pyridyl-2-(*p*-tolyl)methane (**3i**): yellow liquid



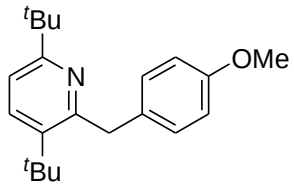
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.28 (s, 9H), 2.23 (s, 3H), 3.98 (s, 2H), 6.80−7.16 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 37.5 (C), 44.6 (CH_2), 112.9 (CH), 116.6 (CH), 128.93 (2CH), 128.94 (2CH), 135.3 (C), 137.4.5(C), 159.3 (C), 160.0 (C), 168.4 (C); IR (neat, cm^{-1}) 2972, 2906, 1706, 1598, 1404, 1361; GC−MS (EI) m/z (relative intensity) 295 (100) [M^+], 280 (46), 266 (3), 166 (2), 77 (2), 57(5); HRMS (EI) m/z calcd for $C_{21}H_{29}N$ [M]$^+$ 295.2300, found 295.2297.

3,6-Di-*tert*-butyl-pyridyl-2-(4-(chloro)phenyl)methane (**3j**): yellow liquid



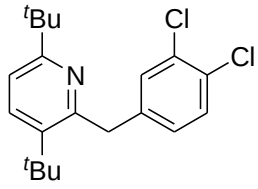
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.28 (s, 9H), 2.23 (s, 3H), 3.98 (s, 2H), 6.80−7.16 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 37.5 (C), 44.6 (CH_2), 112.9 (CH), 116.6 (CH), 128.93 (2CH), 128.94 (2CH), 135.3 (C), 137.4.5(C), 159.3 (C), 160.0 (C), 168.4 (C); IR (neat, cm^{-1}) 2972, 2906, 1706, 1598, 1404, 1361; GC−MS (EI) m/z (relative intensity) 315 (58) [M^+], 300 (100), 243 (2), 125 (5), 91 (4), 79 (1), 77 (2), 57(4); HRMS (EITOF) m/z calcd for $C_{20}H_{26}ClN$ [M]$^+$ 315.1754, found 315.1751.

3,6-Di-*tert*-butyl-pyridyl-2-(4-(methoxy)phenyl)methane (**3k**): yellow liquid



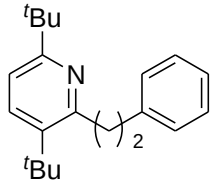
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.30 (s, 9H), 3.65 (s, 3H), 3.99 (s,2H), 6.72− 7.18 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.6 (CH_3), 34.7 (C), 37.4 (C), 43.8 (CH_2), 55.1 (CH_3), 113.6 (CH), 116.7 (CH), 127.8 (2CH), 130.0 (2CH), 132.3 (C), 134.5 (C), 157.9 (C), 159.4, 168.1 (C); IR (neat, cm^{-1}) 2970, 2904, 1598, 1361, 1176; GC−MS (EI) m/z (relative intensity) 311 (100) [M+], 297 (56), 281 (1), 253 (19), 194 (1), 148 (1), 92 (2), 77 (2); HRMS (EI) m/z calcd for $C_{21}H_{29}NO$, [M]$^+$ 311.2249, found 311.2256.

3,6-Di-*tert*-butyl-pyridyl-2-(3,4-(dichloro)phenyl)methane (**3l**) : yellow liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.27 (s, 9H), 3.94 (s, 2H), 6.81−7.40 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.7 (CH_3), 34.8 (C), 37.5 (C), 43.9 (CH_2), 113.4 (CH), 116.7 (CH), 127.8 (CH), 128.6 (CH), 130.0 (CH), 131.1 (C), 131.9 (C), 140.6 (C), 157.6 (C), 160.5 (C), 168.8 (C); IR (neat, cm^{-1}) 2966, 2868, 1598, 1548, 1471, 1215; GC−MS (EI) m/z (relative intensity) 349 (49) [M^+], 334 (100), 2314 (1), 307 (84), 292 (14), 204 (1), 158 (7), 144 (2), 77 (2), 91 (4), 57(1); HRMS (EI) m/z calcd for $C_{20}H_{25}{}^{35}Cl^{37}ClN$ [M]$^+$ 351.1335, found 351.1136; HRMS (EI) m/z calcd for $C_{20}H_{25}Cl_2N$ [M]$^+$ 349.1364, found 349.1342.

3,6-Di-*tert*-butyl-2-phenethylpyridine (**3m**) : yellow liquid



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.31 (s, 9H), 3.00 (s, 4H), 6.73−7.19 (m, 7H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 35.8 (CH_2), 37.8 (C), 40.0 (CH_2), 112.9 (CH), 116.9 (CH), 125.6 (2CH), 128.1 (2CH), 128.5 (CH), 134.5 (C), 142.1 (C), 149.2 (C), 168.1 (C); IR (neat, cm^{-1}) 2962, 2904, 1598, 1409, 1361; GC−MS (EI) m/z (relative intensity) 295 (100) [M^+], 238 (5), 218 (37), 191 (13), 105 (2), 77 (2), 57(3); HRMS (EI) m/z calcd for $C_{21}H_{29}N$ [M]$^+$ 295.2300, found 295.2306.

6-5. Reference

(1) (a) Zeni, G.; Larock, R. C. *Chem. Rev*. **2004**, *104*, 2285. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627 and references therein.

(2) (a) Andrade, B. W. D.; Thompson, M. E.; Forrest, S. R. *Adv. Mater*. **2002**, *14*, 147. (b) Wong, W.-Y.; Zhou, G.-J.; Yu, X.-M.; Knowk, H.-S.; Tang, B.-Z. *Adv. Mater*. **2006**, *16*, 838 and references therein.

(3) (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455. (b) Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc*. **2012**, *134*, 3643 and references therein.

(4) (a) Burnett, B. J.; Barron, P. M.; Hu, C.; Choe, W. *J. Am. Chem. Soc*. **2011**, *133*, 9984. (b) Park, H. J.; Cheon, Y. E.; Suh, M. P. *Chem.Eur. J*. **2010**, *16*, 11662 and references therein.

(5) Selected reviews for the systhesis of pyridines from transitionmetal-catalyzed [2 + 2 + 2] cycloaddition reaction: (a) Vollhardt, K. P. C. *Angew. Chem.* **1984**, *96*, 525;(b) *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (c) Bönnemann, H. *Angew. Chem*. **1985**, *97*, 264;(d) *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248. (e) Varela, J. A.; Saá, C. *Chem. Rev*. **2003**, *103*, 3787. (f) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev*. **2011**, *40*, 3430.

(6) Selected examples for Co-catalyzed [2 + 2 + 2] cycloaddition to form pyridines: (a) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Chem. Commun*. **1973**, 280. (b) Goswami, A.; Ohtaki, K.; Kase, K.; Ito, T.; Okamoto, S. *Adv. Synth. Catal*. **2008**, *350*, 143. (c) Kase, K.; Goswani, A.; Ohtaki, K.; Tanabe, E.; Saino, N.; Okamoto, S. *Org. Lett*. **2007**, *9*, 931. (d) Hapke, M.; Kral, K.; Fischer, C.; Spannenberg, A.; Gutnov, A.; Redkin, D.; Heller, B. *J. Org. Chem*. **2010**, *75*, 3993.

(7) Selected examples for Rh-catalyzed [2 + 2 + 2] cycloaddition to form pyridines: (a) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem*. **2006**, 3917. (b) Komine, Y.; Tanaka, K. *Org. Lett*. **2010**, *12*, 1312.

(8) Examples for Ir-catalyzed [2 + 2 + 2] cycloaddition to form pyridines: Onodera, G.; Shimizu, Y.; Kimura, J.; Kobayashi, J.; Ebihara, Y.; Kondo, K.; Sakata, K.; Takeuchi, R. *J. Am. Chem. Soc*. **2012**, *134*, 10515.

(9) Selected examples for Ni-catalyzed [2 + 2 + 2] cycloaddition to form pyridines: (a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc*. **2005**, *127*, 5030. (b) Kumar, P.; Prescher, S.; Louie, J. *Angew. Chem., Int. Ed*. **2011**, *50*, 10694.

(10) Selected examples for Ru-catalyzed [2 + 2 + 2] cycloaddition to form pyridines: (a) Varela, J. A.; Carlos, L.; Saá, C. *J. Org. Chem*. **2003**, *68*, 8595. (b) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem.Eur. J*. **2006**, *12*, 5618.

(11) Selected examples for Fe-catalyzed [2 + 2 + 2] cycloaddition to form pyridines: (a) Souza, B. R. D.; Lane, T. K.; Louie, J. *Org. Lett*. **2011**, *13*, 2936. (b) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 7162.

(12) Selected examples for Ti-mediated [2 + 2 + 2] cycloaddition to form pyridines: (a) Suzuki, D.;

Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **2002**, *124*, 3518. (b) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc*. **2005**, *127*, 7774.

(13) Selected examples for Zr-mediated [2 + 2 + 2] cycloaddition to form pyridines: (a) Takahashi, T.; Tsai, F.-Y.; Kotora, M. *J. Am. Chem. Soc*. **2000**, *122*, 4994. (b) Takahashi, T.; Tsai, L. Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, M.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.

(14) Examples for Ta-mediated [2 + 2 + 2] cycloaddition to form pyridines: Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett*. **1995**, 851.

(15) Satoh, Y.; Yasuda, K.; Obora, Y. *Organometallics* **2012**, *31*, 5235.

(16) (a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc*. **1987**, *109*, 6551. (b) Hartung, J. B.; Pedersen, S. F. *J. Am. Chem. Soc*. **1989**, *111*, 5468. (c) Obora, Y.; Kimura, M.; Ohtake, T.; Tokunaga, M.; Tsuji, Y. *Organometallics* **2006**, *25*, 2097 and references therein.

(17) (a) Obora, Y.; Takeshita, K.; Ishii, Y. *Org. Biomol. Chem*. **2009**, *7*, 428. (b) Satoh, Y.; Obora, Y. *Org. Lett.* 2011, *13*, 2568. (c) Satoh, Y.; Obora, Y. *J. Org. Chem*. **2011**, *76*, 8569.

(18) (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (b) Oshiki, T.; Nomoto, H.; Tanaka, K.; Takai, K. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 1009 and references therein.

(19) (a) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (b) Arai, S.; Takita, S.; Nishida, A. *Eur. J*. Org. Chem. **2005**, 5262. (c) Oh, K.; W. Kanabe, E. *Tetrahedron* **2009**, *65*, 2966.

(20) Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. *J. Organomet. Chem.* **2006**, *691*, 4434.

(21) $Ph_2SiCl(OMe)$ was analyzed by using the ^{29}Si NMR (DEPT) analysis, GC, and GC−MS. ^{29}Si NMR (DEPT) analysis of pure $Ph_2Si(OMe)_2$ shows a peak at −28.55 ppm. Conversely, the ^{29}Si NMR of the reaction mixture consisting of $NbCl_5$, Zn and $Ph_2Si(OMe)_2$ (as prepared in this reaction) exhibits a low-field shift of this peak to −11.07 ppm (ref 22; $Me_3Si(OMe)$ 17.0 ppm, Me_3SiCl 29.4 ppm).

(22) (a) Hunter, B. K.; Reeves, L W. *Can. J. Chem*. **1967**, *46*, 1399. (b) Schraml, J.; Chvalovsky, V.; Magi, M.; Lippmaa, E. *Collect. Czech. Chem. Commun.* **1979**, *44*, 854.

(23) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoeneback, F.; Zhou, S.; Turner, A. T. *Org. Lett.* **2008**, *10*, 1227.

(24) Knoll, K.; Shcrock, R. R.. *J. Am. Chem. Soc*. **1989**, *111*, 7989.

Chapter 7

General Conclusion

In this thesis, I have developed the use of low-valent niobium catalyst for intermolecular [2 + 2 + 2] cycloaddition reactions.

1,3-Cyclohexadiene derivatives are an important class of cyclic conjugated diene compounds in Diels-Alder reaction and polymerization reaction. Therefore, development of an efficient synthetic methodology of 1,3-cyclohexadienes is very important. Transition-metal-catalyzed intermolecular cycloaddition by the reaction of two molecules of alkyne and one molecule of alkene is one of the simplest and atom-economical methods for preparing 1,3-cyclohexadiene derivatives. However, this methodology mainly leads to the cyclotrimerization of alkynes in preference to the desired cross-cyclotrimerization between alkynes and alkenes.

In Chapters 2-4, I have developed a low-valent Nb catalyzed [2 + 2 + 2] intermolecular cross cycloaddition of alkynes and alkenes, which resulted in substituted-1,3-cyclohexadienes as products.

In Chapter 2, I have developed a new protocol for highly chemo- and regioselective reaction of cross cycloaddition of terminal alkynes and α,ω-dienes, leading to 5-ω-alkenyl-1,3-cyclohexadienes in high to excellent yields. In addition, I found that the 1,3-cyclohexadienes having ω-alkenyl substitutent can be easily converted to the ω-acetyl group. In this reaction, oxidative cycloaddition of two molecules of terminal alkyne towerd to low-vlent Nb(III) center gives niobacyclopentadiene intermediate. Subsquently, niobacyclopentadiene intermediate reacts with α,ω-dienes to give 5-ω-alkenyl-1,3-cyclohexadienes.

In Chapter 3, three-component intermolecular [2 + 2 + 2] cyloaddition of terminal alkynes, internal alkynes, and 1-alkenes was achieved by using $NbCl_3$(DME) catalyst. In addition, I found that 3,4,5-trisubstituted-1,3-cyclohexadienes have been prepared by desilylation from trialkylsilyl-substituted-1,3-cyclohexadienes. Here, oxidative cycloaddition of one terminal alkyne and one terminal alkene to the low-valent Nb ceter initiates the reaction to give niobacyclopentene intermediate. Subsquently, internal alkyne inserts into niobacyclopentene intermediate to form niobacycloheptadiene intermediate. Then, tetrasubstituted-1,3-cyclohexadiene derivatives were obtained by reductive elimination of Nb species.

In Chapter 4, I found that novel low-valent niobium was generated by using of $NbCl_5$ and hydrosilanes as reducing agents. I also demonstrate that the low-valent niobium shows high catalytic activity of the synthesis of 1,3-cyclohexadienes from terminal alkynes and alkenes.

Pyridines and pyrimidines are an important class of *N*-heterocyclic compounds. These compounds are key structure in many natural products, biologically active substances, functional materials, and ligands. Among the methods available for the synthsis of these compounds, the

transition-metal-catalyzed cycloaddition reaction of alkynes and nitriles is of particular importance.

In Chapters 5 and 6, I found that newly *N*-heterocyclic compounds were obtaind by the reaction of akynes and nitriles in the presence of Nb complexes.

In Chapter 5, I have developed a pratical, general, and efficient method for the synthesis of poly substituted pyrimidine derivatives. In this study, I found that pyrimidine derivatives were obtained by reaction of two molecules of nitrile and one molecule of alkyne in the presence of $NbCl_5$ complex. Here, benzonitrile is activated by $NbCl_5$ to form *N*-benzylidenebenzamidine. Subsequent cycloaddition of *N*-benzylidenebenzamidine with phenylacetylene on the benzylidene carbon results in the formation of 2,4,6-triphenylpyrimidine. The synthetic method is the first example of synthsis of pyrimidines by transition-metal-mediated cycloaddition of alkynes and nitrirles.

In Chapter 6, I reported $NbCl_5$ / Zn / $Ph_2Si(OMe)_2$ catalyzed [2 + 2 + 2] cycloaddition of two molecules of *tert*-butylacetylene and one molecule of nitrile, leading to pyridine derivatives. On the basis of investigation of reaction mechanism, cycloaddition of alkynes and nitriles proceeded via niobacyclopentadiene intermediate. The present synthetic method is the first example of synthesis of pyridines by early-transition-metal-catalyzed cycloaddition of alkynes and nitrirles.

I wish that the reported reactions in this thesis will indicate that low-valent niobium complexes found to be effectively utilized for catalysts in organic and industrial chemistry. I wish that the Nb-catalyzed reactions will open the way to an interesting new domain of organic transformation in near future.

List of Publications

I. The present Thesis is composed of the following papers.

Chapter 2

(1)"$NbCl_3$-catalyzed Intermolcular [2+2+2] Cycloaddition of Alkynes and α,ω-Dienes: Highly Chemo- and Regioselective Formation of 5-ω-Alkenyl-1,4-substituted-1,3-cyclohexadiene Derivatives"
Yasushi Obora, Yasushi Satoh, Yasutaka Ishii
J. Org. Chem. **2010**, *75*, 6046-6049.

Chapter 3

(2)"$NbCl_3$-catalyzed Three-component [2+2+2] Cycloaddition Reaction of Terminal Alkynes, Internal Alkynes, and Alkenes to 1,3,4,5-Tetrasubstituted 1,3-Cyclohexadienes"
Yasushi Satoh, Yasushi Obora
Org. Lett. **2011**, *13*, 2568-2571.

Chapter 4

(3)"Active Low-valent Niobium Catalysts from $NbCl_5$ and Hydrosilanes for Selective Intermolecular Cycloadditions"
Yasushi Satoh, Yasushi Obora
J. Org. Chem. **2011**, *76*, 8569-8573.

Chapter 5

(4)"Strategy for the Synthesis of Pyrimidine Derivatives: $NbCl_5$-mediated Cycloaddition of Alkynes and Nitriles"
Yasushi Satoh, Kaoru Yasuda, Yasushi Obora
Organometallics **2012**, *31*, 5235-5238.

Chapter 6

(5)"Low-valent Niobium-catalyzed Intermolecular [2+2+2] Cycloaddition of *tert*-Butylacetylene and Arylnitriles to Form 2,3,6-Trisubstituted-pyridine Derivatives"
Yasushi Satoh, Yasushi Obora
J. Org. Chem. **2013**, *78*, 7771-7776.

II. Following publications are not included in this Thesis.

(6)“Early Transition Niobium Compounds in Organic Transformation–From Stoichiometric Reaction to Catalytic Reaction” [Review]
Yasushi Satoh, Yasushi Obora
有機合成化学協会誌, Submitted.

(7)“Synthesis of Arylacetonitrile Derivatives; Ni-catalyzed Reaction of Benzyl Chlorides and Trimethylsilyl Cyanide under Base Free condition”
Yasushi Satoh, Yasushi Obora
In Preparation

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