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Catalytic Enantioselective Conjugate Addition of Trimethylsilylacetylene to 2-Cyclohexen-1-one

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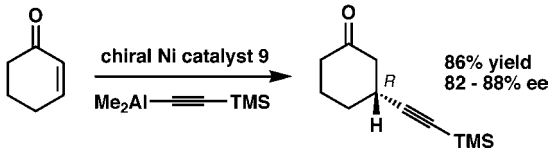
ABSTRACT



The first example of catalytic asymmetric conjugate addition of TMS-acetylene to a cyclic α,β-enone has been accomplished using the chiral bisoxazoline-Ni complex 9 as catalyst and dimethylalumino TMS-acetylide and 2-cyclohexen-1-one as reactants.

The conjugate addition of alkynyl groups to cyclic α,β-unsaturated ketones has been an elusive synthetic challenge. Organocuprates, the most commonly used reagents for 1,4-addition of alkyl and alkenyl groups to α,β-enones, cannot be employed in β-alkynylation reactions because of the inertness that arises from copper's strong binding to alkynyl ligands.[1] Indeed, the strength of the sp-carbon-Cu(I) bond has allowed alkynyl groups to serve as nontransferable ligands in mixed cuprate reagents.[2] β-Alkynylated ketones have previously been accessed indirectly from β-stannyl alkenyl cuprates[3] rather than directly except for the special case of acyclic α,β-enones, which undergo reaction with ethynyl boranes, alanes, or boronates.[4] This method is strictly limited to acyclic enones capable of adapting an *s-cis* conformation that can lead to reaction by way of a cyclic transition state. For the substrates fixed in an *s-trans* conformation, such as 2-cyclohexen-1-one, the enantioselective conjugate addition of alkynyl groups has remained as an unmet challenge.

Two methods have been reported for the *nonenantioselective* conjugate addition of alkynyl groups to cyclic α,β-enones, one using organozinc reagents[5] and the other organoaluminum acetylides in the presence of a blood red Ni(I) catalyst generated in situ by a reduction of $Ni(acac)_2$ with an equimolar amount of DIBAL-H.[6] Following up on the latter approach we have investigated the asymmetric conjugate addition of alkynyl groups to cyclic α,β-enones in the presence of a chiral Ni catalyst using trimethylsilylacetylene and 2-cyclohexenone as a test case.

We chose to start with a Ni(II) complex **2** possessing one acetylacetonate and one (*S*,*S*)-bisoxazoline ligand **1**, as shown in Figure 1. Complex **2** was prepared by reaction of $Ni(acac)_2$ with 1 equiv of the C_2-symmetric bisoxazoline **1**. Complex **2** so made was obtained as a dark-purple solid that was stable to air and moisture at room temperature and pure by ^1H NMR analysis. It was used directly without further purification.

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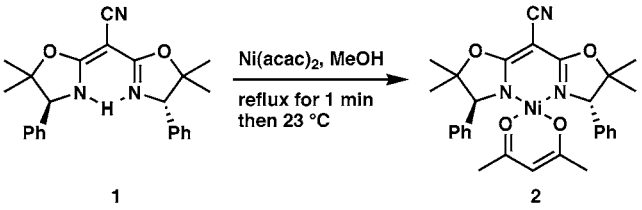


Figure 1. Preparation of the "mixed" Ni(II) catalyst **2**.

Complex **2** was readily reduced by 1 equiv of DIBAL-H in DCM at −40 °C to give a deep red solution of what is probably a Ni(I) species. This complex was immediately treated with dimethylaluminum TMS-acetylide followed by 2-cyclohexen-1-one (Figure 2). The alkynylated product **3**

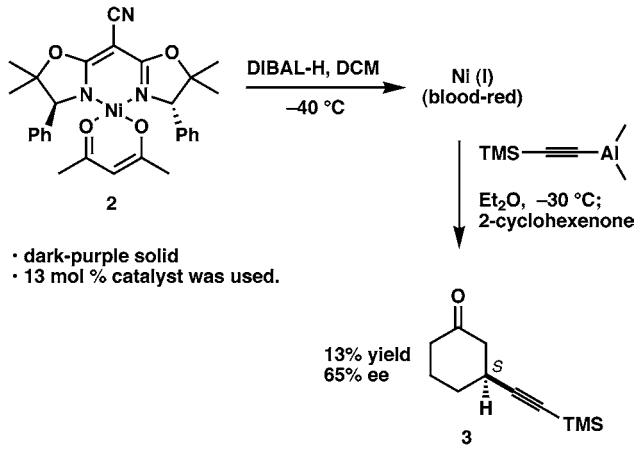


Figure 2. Ni(I)-catalyzed asymmetric conjugate addition of $TMSCCAlMe_2$ to 2-cyclohexenone.

was isolated in 13% yield (13 mol % catalyst loading) and shown by GC analysis (Cyclosil B) to have 65% enantiomeric excess (ee). The absolute configuration of **3** was established by desilylation (K_2CO_3−MeOH) and hydrogenation (1 atm H_2, Pd−C) to give the known levorotatory (*S*)-3-ethyl cyclohexanone.

Despite substantial effort to optimize the conditions for this Ni(I)-catalyzed reaction, we were unable to increase the yield or the selectivity. These efforts led us to investigate the possibility of using complex **2** directly without reduction, which appeared to be reasonable since Ni(II)-catalyzed conjugate addition of organozinc reagents to 2-cyclohexenones is well-known. Although, the application of Ni(II) catalysis to 1,4-addition of alkynyl groups has not been reported, to the best of our knowledge, a rational mechanistic pathway for such a Ni(II)-catalyzed reaction can be envisaged, as is illustrated in Figure 3 for complex **2**. This pathway involves the carbometalation of the α,β-enone by intermediate **4** as a key step.

It is worth mentioning that Ni(II)-catalyzed 1,4-addition of alkynyl groups to 2-cyclohexenone has been previously

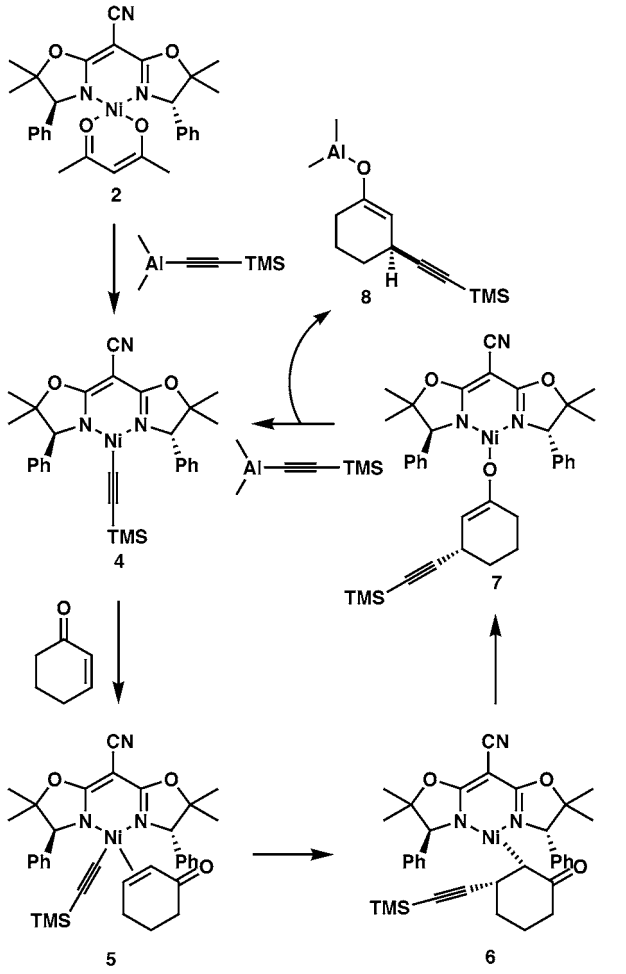


Figure 3. Possible catalytic cycle for the Ni(II)-catalyzed conjugate addition of $TMSCCAlMe_2$ to 2-cyclohexenone.

examined by Schwartz's group.[6b] They reported that Ni(acac)$_2$ in the absence of DIBAL-H did not function as well as Ni(I) in the 1,4-addition of dimethylaluminum acetylides. Instead they obtained an equimolar amount (based on nickel) of coupled diacetylene, which presumably resulted from a double ligand exchange reaction of Ni(acac)$_2$ with two molecules of the aluminum acetylide followed by reductive elimination to form lower valent Ni species. We considered the possibility that the formation of diacetylene might be reduced because the bisoxazoline ligand is bound to the nickel more tightly than acetylacetonate so as to allow clean formation of the required intermediate **4** without the formation of a bisalkynyl Ni(II) complex.

Our initial experiment on the Ni(II)-catalyzed conjugate addition of TMS-acetylide to 2-cyclohexenone is summarized in Figure 4. Catalyst **2** (10 mol % relative to 2-cyclohexenone) was added to the solution of dimethylaluminum TMS-acetylide in diethyl ether (2 equiv relative to 2-cyclohexenone) at 0 °C. The Michael acceptor 2-cyclohexenone was then added, and the mixture was stirred for 2 h at the same temperature. The conjugate adduct **3** was isolated in 51% yield[7] and with 61% ee.

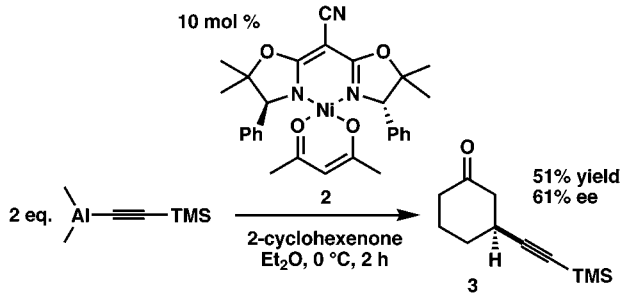


Figure 4. Ni(II)-catalyzed conjugate addition of dimethylaluminum TMS-acetylide to 2-cyclohexenone.

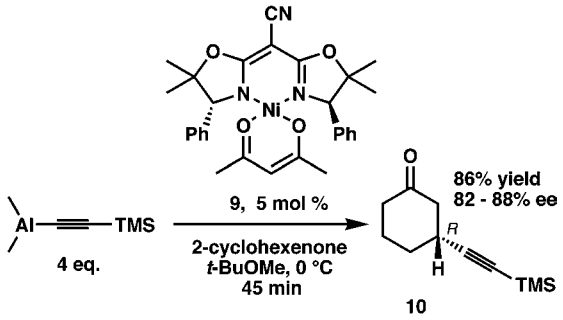
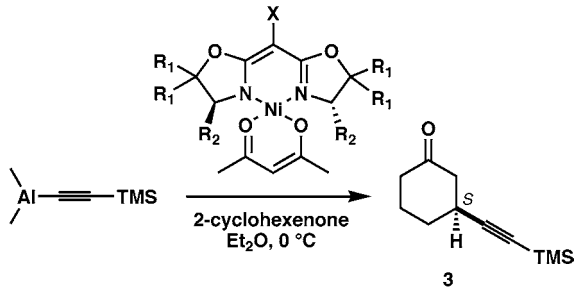


Figure 5.

We then examined the Ni(II)-catalyzed conjugate addition with several other bisoxazolines (Table 1). This study showed

Table 1.



entry	R_1	R_2	X	yield (%)	ee (%)
1	Me	Ph	CN	51	61
2	H	Ph	CN	48	44
3	H	*t*-Bu	CN	46	0
4	H	*i*-Pr	CN	47	5
5	H	benzyl	CN	43	9
6	H	1-naph	CN	44	17
7	H	2-naph	CN	45	27
8	Me	Ph	Tf	54	14
9	Me	Ph	Ts	45	10
10	Me	Ph	F	41	0
11	Me	Ph	CO_2Me	33	5

that **2** (R_1 = Me, R_2 = Ph, X = CN) is the most selective catalyst among those tested. Aromatic groups (particularly phenyl) at R_2 were superior to other appendages (entries 3−7). It is noteworthy that better results were obtained with X = CN than with other electron-withdrawing groups (entries 8−11). The reaction was also very sensitive to other variables. The purity of $TMSCCAlMe_2$, which was generated in situ by reaction of TMSCCLi with Me_2AlCl, was critical. Any excess of either lithium acetylide or Me_2AlCl led to **3** with lower yield and ee. Complete reaction of the lithium acetylide with Me_2AlCl is therefore essential (we found that 5 h at 10 °C was required). The yields and enantioselectivity also varied with solvent. Methyl-*tert*-butyl ether was found to be distinctly superior to Et_2O, THF, toluene, or mixtures of these. Under optimal conditions, which involved the use of 4 equiv of $TMSCCAlMe_2$ in *t*-BuOMe at 0 °C for 45 min and 5 mol % of the *R,R*-catalyst **9** (prepared from *ent*-**1**) with addition of 2-cyclohexenone over less than a min, the *R*-conjugate addition product **10** was produced in 86% yield and with 82−88% ee (Figure 5).[8]

In contrast to the results described above using the enantiomeric nickel complexes **2** and **9**, we have not been able to effect conjugate addition of TMS acetylene to 2-cyclohexenone using different variants of the recently developed methodology for enantioselective rhodium-BINAP-catalyzed conjugate addition of aryl groups to α,β-enones.[9] We believe that the enantioselective nickel-catalyzed alkynylation exemplified herein deserves further investigation to define fully the scope, mechanistic pathway, and optional catalytic ligand. It is, nonetheless and as it stands, a practical process with no current alternatives. Illustrative procedures are given in refs 10−12.

(7) The major contaminants in the crude product were formed by further reactions of the aluminum enolate **8** with 2-cyclohexenone. The yield can be improved (up to 68%) by slow addition of 2-cyclohexenone.

(8) It is very important that the formation of $TMSCCAlMe_2$ be complete (ca. 5 h at 10 °C required) and that exact 1:1 stoichiometry of TMSCCLi and Me_2AlCl be used. Any excess of Me_2AlCl catalyzes the conjugate addition to form racemic β-ethynylated cyclohexanone. Any excess of TMSCCLi rapidly destroys the catalyst. Using these optimal conditions the rate of addition of 2-cyclohexanone is no longer critical and the ee of the product falls in the 82−88% ee range.

(9) See: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Shintani, Y.; Takunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.

(10) **Preparation of Cyanobisoxazoline *ent*-1 (*R,R*-Configuration).** A 250-mL round-bottom flask was equipped with a Dean−Stark apparatus, and 100 mL of dry xylenes was added under a nitrogen atmosphere. Then 2.1 g of (*R*)-1,1-dimethyl-2-amino-2-phenylethanol (12.7 mmol) and 0.96 mL of diethyl malonate (6.3 mmol) were added. The reaction mixture was heated at reflux with magnetic stirring overnight, and 100 mg of dibutyltin dichloride was added. Heating at reflux was continued with removal of water by the Dean−Stark trap for 2 days at which time TLC analysis (hexanes−ethyl acetate, 1:2) indicated completion of the reaction. Removal of solvent by distillation gave a yellow syrup that was purified by column chromatography (hexanes−ethyl acetate, 1:2) to provide 1.77 g (4.9 mmol, 78%) of the corresponding bisoxazoline. A solution of 800 mg (2.2 mmol) of this bisoxazoline in 10 mL of anhydrous THF was stirred at −78 °C under a nitrogen atmosphere and treated with tetramethylethylenediamine (TMEDA) (0.3 mL, 2 mmol) and 1.6 mL (3.5 mmol) of *n*-BuLi in hexanes at the same temperature. The resulting brown reaction mixture was stirred for 1 h at −78 °C, and 635 mg (3.5 mmol) of tosyl cyanide was added in one portion (the brown color faded immediately). The reaction mixture was allowed to warm to 0 °C, stirred for 1 h, and then diluted with Et_2O and

In conclusion, the first example of an asymmetric conjugate addition of an alkynyl group to a cyclic α,β-enone has been achieved with dimethylalumino TMS-acetylide, 2-cyclohexenone, and a catalytic amount of the chiral Ni(II) complex **9** (or the enantiomer **2**) in *t*-BuOMe under carefully controlled conditions.

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saturated NH_4Cl solution. The organic layer was dried with $MgSO_4$ and concentrated in vacuo, and the residue was purified by column chromatography (hexanes−ethyl acetate, 2:1) to provide 652 mg (1.68 mmol, 77%) of the (*R*,*R*)-cyano-bisoxazoline *ent*-**2**.

(11) **Preparation of Ni(II) Complex 9.** A solution of 193 mg of cyanobisoxazoline *ent*-**1** in 2 mL of MeOH was stirred at 23 °C under a nitrogen atmosphere. Then 154 mg of $Ni(acac)_2$ was added in one portion; an immediate color change from green to dark purple was observed. The reaction mixture was then heated at reflux for 1 min and cooled to room temperature. The reaction mixture was stirred for 12 h at ambient temperature under a nitrogen atmosphere. The solvent was removed in vacuo, and the remaining solid was dissolved in ethyl ether. Insoluble material was removed by filtration, and the dark-purple filtrate was concentrated in vacuo to provide analytically pure **9** as a dark-purple solid (201 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (5H, bs), 7.27−7.31 (5H, t, $J = 7.3$), 4.95 (1H, s), 4.05 (2H, s), 1.49 (6H, s), 1.38 (6H, s), 0.83 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 185.7, 167.6, 141.3, 128.4, 127.5, 127.0, 101.2, 87.2, 71.7, 28.8, 24.8, 24.1. FT-IR (thin film, cm^{-1}): 2359.8, 2340.4, 1624.3, 1521.0, 1088.6.

(12) **Enantioselective Synthesis of 10 using Complex 9.** A solution of *n*-BuLi (1.1 mL, 2.5 M solution in hexanes) was added to 2 mL of anhydrous *t*-BuOMe with stirring at −78 °C under nitrogen. Then 0.35 mL of TMS-acetylene was added dropwise, and the reaction mixture was stirred at the same temperature for 30 min. It was then transferred via a cannula to a solution of 1.9 mL of dimethylaluminium chloride (1.0 M solution in hexanes) in 1 mL of *tert*-butylmethyl ether at 0 °C. Upon the addition a slow precipitation of LiCl was observed. Then 5 mg of lithium iodide was added, and the reaction mixture was stirred for 5 h at 10 °C. The reaction mixture was cooled to 0 °C, and 20 mg (0.036 mmol, 5 mol %) of (*R*,*R*)-Ni(II) catalyst **9** was added. Then 70 μL (0.7 mmol) of 2-cyclohexen-1-one was added immediately. The reaction mixture was stirred at 0 °C for 45 min and monitored by TLC analysis (hexanes−ethyl acetate, 4:1). Ethyl ether and 0.3 mL of saturated $NaHCO_3$ solution were added, and the mixture was stirred for 10 min at ambient temperature. The ether layer was dried with $MgSO_4$ and filtered through a pad of Celite. Concentration and purification by column chromatography on silica gel (hexanes−ethyl acetate, 5:1) provided 116 mg (86%) of **10** as a colorless oil, $[\alpha]^{20}_D = -0.266$ (*c* 1, $CHCl_3$). The enantiomeric purity (82% ee) was determined by GC analysis using a chiral Cyclosil B column. (The oven temperature was 50 °C for 8 min at start and increased by 2 °C/min). The retention times of **10** and its enantiomer **3** were 47.225 and 47.516 min.