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Ni(II)-Catalyzed Enantioselective Conjugate Addition of Acetylenes to α,β-Enones

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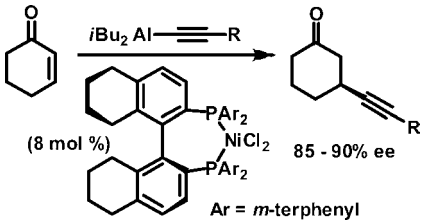
ABSTRACT



Alkynylaluminum reagents undergo enantioselective conjugate addition to cyclic α,β-enones in the presence of chiral bisphosphine complexes of Ni(II).

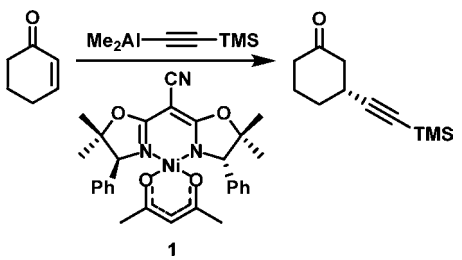
In 2004, we reported a catalytic enantioselective conjugate addition of a terminal acetylene to an α,β-unsaturated enone, as illustrated in Scheme 1.[1] The key to the success of this method was the use of the chiral Ni(II) catalyst **1**. One significant finding from this research was that the Ni(I) cyanobisoxazoline complex corresponding to **1** was much less effective since its use led to very low yields and poor enantioselectivity.

In the meantime, T. Hayashi and his group at Kyoto University have described the use of chiral bisphosphine Rh(I) catalysts (5 mol %) to effect asymmetric conjugate addition of trialkylsilylacetylenes to α,β-enones.[2]

More recently, we returned to the less expensive Ni-based catalytic system to develop other catalysts and to obtain a better understanding of the mechanistic pathway of Ni(II)-catalyzed alkynylation of α,β-enones.

The focus of the present work has been the use of chiral bisphosphine Ni(II) complexes as catalysts. We found in preliminary experiments that although the Ni(0) complex $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) catalyzes the rapid and efficient conjugate addition of alkynyldimethylaluminum reagents[3] to α,β-enones Ni(0) complexes with chiral bisphosphines or chiral bicyclo[2.2.1]heptadienes are not effective catalysts.

Scheme 1



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(1) Kwak, Y.-S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385–3388.

(2) (a) Nishimura, T.; Tokuji, S.; Sawano, T.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3222–3225. (b) Nishimura, T.; Guo, X.-X.; Uchiyama, M.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576–1577. (c) Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14158–14159.

(3) Alkynyldialkylaluminum reagents were prepared from the corresponding alkynyllithium and dialkylaluminum chloride. In line with the observation made in the previous study (ref 1), the exact 1:1 stoichiometry of the reagents is necessary to achieve high yields of the conjugate addition products.

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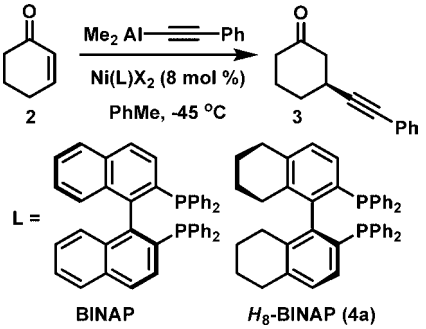
Initial experiments with various classes of ligands indicated that diphosphines of the BINAP family showed promise with Ni(II) (Scheme 2). The complex of BINAP with $NiBr_2$ produced the alkynylation product **3** with 7:1 enantioselectivity (75% ee) but in only 26% yield. Since the nickel(II) complexes of BINAP are only sparingly soluble in toluene, the more soluble H_8-BINAP (**4a**) was employed. This led to an improvement in yield to 42% with a slight drop in enantioselectivity (72% ee).

Scheme 2

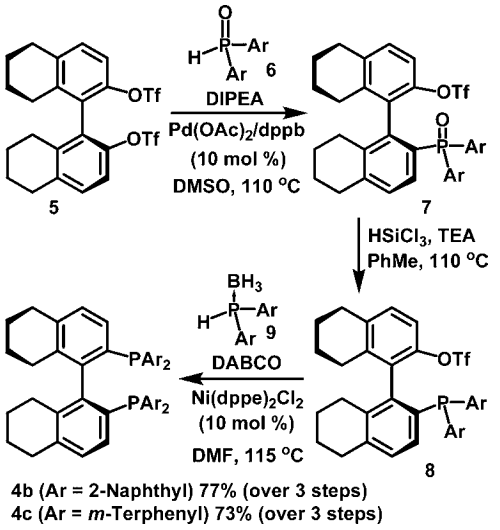


Experiments with other solvents showed that while the use of more polar solvents, such as dichloromethane and tetrahydrofuran, affords ketone **3** in higher yields the enantioselectivity is diminished. Toluene emerged as the solvent of choice for this process, the rate of which was very slow in hexane, partly due to poor solubility of the catalyst. The counterion in the nickel salt also influenced the reaction outcome. Nickel acetate or triflate failed to catalyze the reaction. The complex of nickel iodide with **4a** proved to be a very efficient catalyst; however, the overall yield of the product **3** was lower than for the bromide, due to condensation of the intermediate enolate with cyclohexenone. This side reaction may be promoted by the high Lewis acidity of dimethylaluminum iodide, which is formed from the alkynylaluminum reagent. Nickel chloride, on the contrary, performed better than the bromide and gave rise to the conjugate addition product **3** in 64% yield and 72% ee.

The influence of the dialkylaluminum unit was studied next. While dimethyl- and diethylaluminum reagents provided comparable results, diisobutyl(phenylethynyl)-aluminum, prepared from phenylethynyllithium and diisobutylaluminum chloride, produced ketone **3** with 75% ee. Use of 2 mol % of the ligand H_8-BINAP (**4a**) resulted in a further increase of enantioselectivity (79% ee). The optimal temperature was found to be −45 °C. Lower temperatures led to very slow reaction, probably as a result of poor catalyst solubility. On the other hand, experiments run at higher temperatures afforded ketone **3** with lower enantiomeric purity. In fact, nearly racemic product was obtained, when the reaction was conducted at room temperature.

Further improvement in enantioselectivity was sought through modification of the bisphosphine ligand. Two new ligands, which contain the octahydrobinaphthalene backbone with bulky aryl substituents on phosphorus atoms, were prepared for this study in three steps from bistriflate **5** (Scheme 3). Palladium-catalyzed coupling[4] of **5** with diarylphosphine oxide **6** yielded the phosphine oxide **7**, which was reduced with trichlorosilane in the presence of triethylamine in toluene. The monophosphines **8** were allowed to react with the diarylphosphine−borane complexes **9** in the presence of a nickel(II) catalyst to give the bisphosphines **4b** (Ar = 2-naphthyl) and **4c** (Ar = *m*-terphenyl) in yields of 77% and 73%, respectively, over three steps. The bisphosphines are crystalline, air-stable solids.

Scheme 3. Synthesis of the Novel Bisphosphine Ligands **4b**,**c**



The catalytic performance of the nickel(II) complex of the 2-naphthyl analogue of H_8-BINAP **4b** proved to be similar to that of the parent ligand, as only a moderate improvement of enantioselectivity (84% ee) was observed. However, the larger *m*-terphenyl ligand **4c** proved to be very efficatious since it afforded the conjugate addition product with 90% ee (71% yield).

Other cyclic enones also undergo efficient alkynylation catalyzed by the Ni(II) complex of the new terphenyl bisphosphine ligand **4c**. Although cyclopentenone appeared to be unsuitable for the reaction, larger cycloalkenones underwent conjugate additions of alkynyl-diisobutylaluminum reagents to form the corresponding ketones with 85−90% ee.

Ni(II) phosphine complexes are known to react with acetylenes under basic conditions to give bis(phosphine)nickel diacetylides.[5] When Ni(BINAP)Br_2 was treated with 2 equiv of phenylethynyllithium, a new peak in the ^{31}P NMR spectrum appeared at δ 40 ppm.

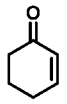
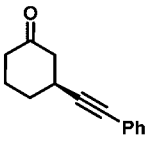
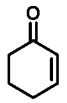
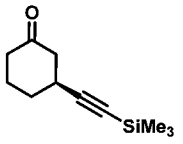
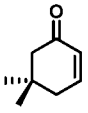
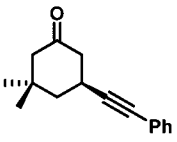
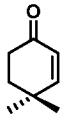
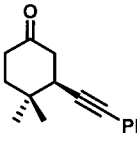
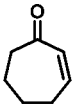
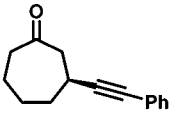
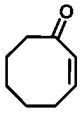
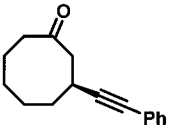
The same peak was present in the spectrum when Ni(BINAP)Br_2 was treated with dimethyl(phenylethynyl)-aluminum,

(4) Henschke, J. P.; Burk, M. J.; Malan, C. J.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300–307.

(5) (a) Nast, R.; Beyer, A. *J. Organomet. Chem.* **1981**, *204*, 267–272. (b) Masai, H.; Sonogashira, K.; Hagihara, N. *J. Organomet. Chem.* **1971**, *26*, 271–276.

indicating that nickel(bisphosphine) diacetylide may be the Ni(II) reagent responsible for the conjugate addition to α,β-enones. When this complex was treated with cyclohexenone and the alkynylaluminum at −45 °C, formation of the ketone **3** with 72% ee was observed. Since the reaction requires the presence of aluminum reagents to proceed, the dialkylaluminum chloride formed during the ligand metathesis with Ni(BINAP)Cl_2 plays a crucial role as an enone activator. Electrophilic attack by the α,β-enone−R_2AlCl complex on the dialkynyl Ni(II) partner can explain absolute stereochemical preference summarized in Table 1.

Table 1. Nickel-Catalyzed Conjugate Additions of Alkynylaluminum Reagents to Cyclic α,β-Enones[a]

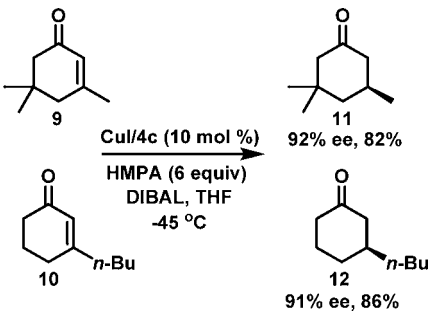
entry	substrate	product	yield/ (ee), %
1			71 (90)
2			69 (85)
3			67 (89)
4			74 (85)
5			63 (86)
6			61 (88)

[a] Reactions were performed with 0.5 mmol of cyclic α,β-enone, Ni(**4c**)Cl_2 (8 mol %), **4c** (2 mol %), and diisobutyl(phenylethynyl)aluminum (1.4 mmol) in toluene at −45 °C for 6 h. Enantiomeric purity (ee) of the products was determined by chiral HPLC.

The bisphosphine **4c** may also be a very useful ligand for other catalytic transformations. Since copper(I)-catalyzed conjugate reduction of enones has been described with chiral bisphosphines being ligands of choice,[6] we studied this application of the new ligand **4c** with diisobutylaluminum hydride (DIBAL) as the hydrogen source.

Gratifyingly, when the isophorone (**9**) and 3-butylcyclohex-2-eneone (**10**) were treated with DIBAL at −40 °C in the presence of CuI, ligand **4c** (10 mol %), and HMPA[7] (6 equiv), rapid conjugate reduction ensued (Scheme 4). The

Scheme 4. CuI/**4c**-Catalyzed Conjugate Reduction of Enones by DIBAL



saturated ketones **11** (92% ee) and **12** (91%) were formed in high yield.[8] DIBAL has not been used previously in the enantioselective conjugate reduction of α,β-enones. It is known that in the absence of catalyst DIBAL effects 1,2-addition to α,β-enones.[7] Interestingly, virtually racemic conjugate reduction product was formed in low yield (10%), when BINAP was used as a ligand under otherwise identical conditions.

In conclusion, the enantioselective conjugate addition of alkynylaluminum reagents catalyzed by Ni(II) complexes of bisphosphine **4c** provides a new and efficient synthesis of enantiomerically enriched cyclic 3-alkynylketones, which are otherwise difficult or expensive to access. The new bisphosphine **4c** is a useful ligand for enantioselective reduction of α,β-enones and probably other applications in enantioselective catalysis.

Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902643W

(6) For recent reviews, see: (a) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927. (b) Lipshutz, B. H. *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 167−187. (c) Rendler, S.; Oestreich, M. *Angew. Chem.* **2007**, *119*, 504−510; *Angew. Chem., Int. Ed.* **2007**, *46*, 498−504.

(7) The beneficial effect of hexamethylphosphoramide on nonenantioselective CuMe-catalyzed conjugate enone reductions by DIBAL was first observed by Saegusa et al.: Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540.

(8) Less then 3% of the racemic alcohol arising form the uncatalyzed 1,2-reduction was formed.