Communication

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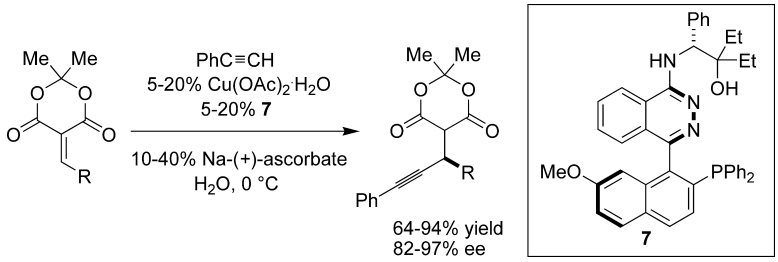


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# Catalytic, Enantioselective, Conjugate Alkyne Addition

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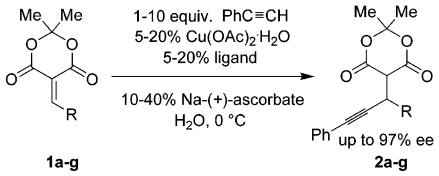
The conjugate addition reaction of carbon nucleophiles to acceptors provides important avenues to access optically active building blocks.[1] Transmetalation of organometallic compounds to the corresponding organocopper reagents is widely employed to ensure regioselective 1,4-addition to α,β-unsaturated carbonyl compounds.[2] Absent from these reagents, however, are the corresponding copper alkynylides, which are, in general, insufficiently reactive for this purpose.[3] Known methods for the conjugate addition of alkynes include the use of boron[4−6] and aluminum[5,7] alkynylides.[8] Recently, catalytic asymmetric variants of these unique reactions have been reported for a limited set of substrates.[9,10] These represent the only examples for this enantioselective reaction, albeit both methods require the stoichiometric formation of a moisture-sensitive metal alkynylide prior to the addition. We have recently reported a novel Cu-catalyzed conjugate addition reaction of aromatic alkynes to Meldrum's acid derived acceptors under very mild reaction conditions.[3,11] In this communication, we document the first example of a catalytic, enantioselective, conjugate addition involving the direct use of terminal acetylenes (eq 1). The addition reactions of **1** to afford **2** take place in aqueous media, without recourse to inert atmosphere. The success of the enantioselective process was enabled by the use of a new class of conveniently accessed P,N-ligands, which we have termed PINAP (Scheme 1).[12]




(1)

In initial investigations of the catalytic, enantioselective addition of acetylenes to Meldrum's acid derived acceptors, we screened a variety of ligand classes, that is, phosphines, such as BINAP, JOSIPHOS, MONOPHOS, MOP, as well as nitrogen donors, as exemplified by PYBOX and BOX.[13] For all but one ligand examined with **1a** (R = *i*-Pr) as a test substrate, the extent of asymmetric induction observed was low, at best 25% ee for tol-BINAP. QUINAP[14] was the singular exception, giving full conversion to product in 42% ee (Table 1, entry 1). Building upon this result proved difficult, as QUINAP analogues bearing structural as well as electronic modifications are not readily prepared. Consequently, we developed PINAP ligands[12] (Scheme 1) which can be accessed in an easy four-step sequence from commercially available starting materials. This project permitted us to examine structural and electronic effects of this new modular class of ligands.

In exploratory studies, we examined the Cu-catalyzed addition of phenylacetylene to **1a** (R = *i*-Pr) employing the simplest member of the PINAP class of ligands derived from optically active α-phenethylamine, namely, **3** and **4** (Table 1). The adduct **2a** was obtained in enhanced optical purity using **3** at 23 °C (69% ee, entry 2). At 0 °C, the enantioselectivity was further improved to 80% ee (entry 3). We found that **3** gave much better results than its diastereomer **4**, which furnished adduct in 37% ee. This behavior

***Scheme 1***

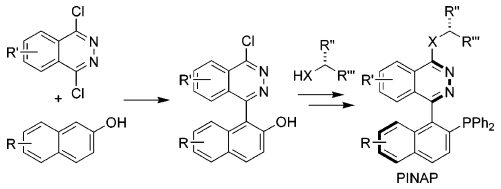
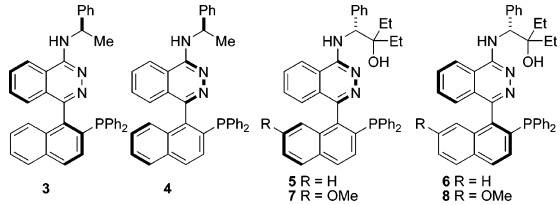



***Table 1.*** PINAP Ligands **3**−**8** in the Screening of the Reaction of PhC≡CH and **1a** to Give **2a** (R = *i*-Pr), as Shown in Eq 1




| entry | ligand | *T* (°C) | *t* (h) | ee[a] (%) | conversion (%) |
|---|---|---|---|---|---|
| 1 | (*R*)-QUINAP | 23 | 5 | 42 (*R*) | 100 |
| 2 | **3** | 23 | 6 | 69 (*S*) | 43[b] |
| 3 | **3** | 0 | 18 | 80 (*S*) | 58 |
| 4 | **4** | 0 | 20 | 37 (*R*) | 33 |
| 5 | **5** | 0 | 11 | 94 (*R*) | 40 |
| 6 | **6** | 0 | 11 | 48 (*S*) | 49 |
| 7 | **7** | 0 | 14 | 95 (*R*) | 100 |
| 8 | **8** | 0 | 14 | 8 (*S*) | 44[b] |

[a] The enantioselectivity was determined by chiral HPLC after conversion to the corresponding anilide by heating in aniline/DMF. The absolute configuration of the major enantiomer of **2a** is given in parentheses. [b] Isolated yield.

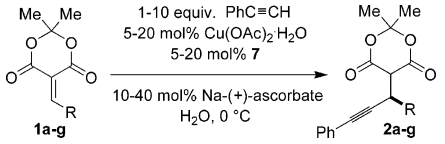
was unanticipated. One would have expected minimal influence by the remote stereocenter, as we have observed for PINAP in other metal-catalyzed reactions studied to date.[12] This strongly suggested a critical role for the chiral amine controlling group, giving rise to matched/mismatched effects. Therefore, we reasoned that its variation would allow fine-tuning of the enantioselectivity.

A set of amines that can be conveniently appended to the PINAP scaffold are the amino alcohols derived from amino acids. In a screening of several simple derivatives (i.e., 2-phenylglycinol, the tertiary alcohols isolated from the addition of MeMgBr, EtMgBr, *n*-PrMgBr, and BnMgBr to phenylglycine methyl ester), the diethyl derivative **5** was singled out by its ability to afford product in high enantioselectivity (94% ee, entry 5), albeit sluggishly (40% conversion after 11 h). Surprisingly, the use of the methoxy-substituted ligand **7** (Table 1, entry 7)[15] resulted in product formation at a significantly faster rate (full conversion after 14 h), while maintaining high enantioselectivity in the process (95% ee).[16] Once again, the atropdiastereomeric ligands **6** and **8** gave, as in the case of **4**, products with dramatically diminished enantioselectivity (entries 6 and 8).

In the optimized procedure, a 1:1 mixture of ligand **7** and $Cu(OAc)_2 \cdot H_2O$[17] is employed at 5−20 mol % loading. In general, because of the heterogeneous nature of the reaction, on 0.25 mmol-scale, excess phenylacetylene (10 equiv) is used. However, the


10.1021/ja052411r CCC: $30.25 

***Table 2.*** Enantioselective Conjugate Addition of Phenylacetylene to the Acceptors **1a**−**g**[a]




| entry | R | *t* (h) | **7** (mol %) | yield (%) | ee(%)[b] |
|---|---|---|---|---|---|
| 1 | *i*-Pr (**1a**) | 14 | 10 | 94 | 95 |
| 2 | $C_6H_{11}$ (**1b**) | 14 | 10 | 81 | 94 |
| 3 | *c*-Pr (**1c**) | 51 | 10 | 79 | 97 |
| 4 | *i*-Bu (**1d**) | 24 | 20 | 85 | 90 |
| 5 | Et (**1e**) | 24 | 20 | 83 | 82 |
| 6 | Ph (**1f**) | 66 | 20 | 64 | 83 |
| 7 | *m*-tol (**1g**) | 66 | 20 | 87 (60)[c] | 90 (98)[c] |
| 8 | *i*-Pr (**1a**) | 14 | 5 | 93 | 94 |

[a] Reactions were run using 10 equiv of phenylacetylene, except entry 8, which was run using 1 equiv. Reactions were run at 0.25 mmol scale, except for entries 6 and 7, which were run at 0.5 mmol scale, and entry 8, which was run at 1.25 mmol scale. [b] The enantioselectivity was determined by chiral HPLC analysis after conversion to the corresponding anilide by heating in aniline/DMF (see Supporting Information). [c] After one recrystallization from EtOAc.

amount of phenylacetylene used can be reduced to 1 equiv already at 1.25 mmol-scale (see below). The scope of the reaction was then examined (Table 2). In the case of $\gamma$-branched acceptors (entries 1−3), the reactions can be conducted with 10 mol % of catalyst. The products **2a**−**c** were obtained in 94−97% ee and 79−94% yield. In the absence of $\gamma$-branching, the acceptors required 20 mol % of catalyst and gave slightly lower selectivities (entries 4 and 5). Acceptors bearing aromatic groups required prolonged reaction times (entries 6 and 7). All the products obtained are crystalline solids (see Supporting Information). As exemplified by **2g** (entry 7), the optical purity could be upgraded by a simple recrystallization (mp 136−137 °C (EtOAc), 90 → 98% ee). The absolute configuration of the adducts was established for **2a** and **2f** by conversion into known compounds; for **2b**, an X-ray structure was obtained of the corresponding 4-bromoanilide derivative (in situ generation of the putative ketene and trapping by the amine: **2b** + 4-bromoaniline, DMF, 100 °C, 1 h).[18]

It should be noted that the reactions we have described are heterogeneous, thus, efficient stirring of the reaction mixture is essential for high conversion. In our current working hypothesis, water does not serve per se as the reaction solvent, but rather as the medium in which the reactive copper species is generated. The conjugate addition reaction itself is believed to take place in the organic phase, namely, phenylacetylene. Importantly, when the reaction is conducted on larger scale, more efficient mixing allows for diminution of the amount of phenylacetylene used. Thus, in the reaction with **1a**, the use of 1 equiv of phenylacetylene furnished **2a** in 93% yield and 94% ee when the reaction was run on 1.25 mmol-scale (250 mg of **1a**) using 5 mol % of **7** (Table 2, entry 8).

Aliphatic alkynes also react under these conditions; for example, the addition of 4-phenyl-1-butyne to **1a** furnishes the corresponding adduct in 29% yield and 68% ee after 24 h at 23 °C using 20% of **7**. Nonetheless, the phenylacetylene adducts we document have immediate value. Similar compounds generated in racemic form by addition of lithium phenylacetylide to a Meldrum's acid acceptor have been shown to be precursors to substances that display broad pharmacological activity as tumor necrosis factor (TNF) inhibitors and gastrin-releasing peptide (GRP) receptor antagonists.[19] The inability to access $\gamma,\delta$-alkynyl acids in optically active form has led to their resolution by preparative chiral HPLC.

We have reported a novel method for the catalytic, enantioselective, conjugate alkyne addition to Meldrum's acid derived acceptors to give adducts in 82−97% ee and useful yields. Importantly, the study has resulted in a unique process for conjugate addition wherein the terminal alkyne undergoes in situ metalation under mild conditions that are catalytic in metal. Moreover, in the context of this reaction-driven study, we have examined PINAP as a ligand. The observations with this new ligand for copper underscore the salient features of PINAP as a modular monophosphine scaffold, whose steric and electronic properties can be tuned in a variety of ways with the aim of optimizing both reaction rate and product enantioselectivity. The ability of Cu−acetylides[20] to participate in enantioselective conjugate additions opens up new possibilities for these carbon−nucleophiles in organic synthesis and sets the stage for additional investigations of these in related processes to provide wide access to useful building blocks.

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**Supporting Information Available:** Experimental procedures as well as full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The relative configuration of the ligand **7** was unambiguously established by X-ray crystallographic analysis (ref 18).
(16) The absolute configuration of the ascorbate has no effect on the asymmetric induction; in the addition to **1a** using (+)-ascorbate, **7** and *ent*-**7** furnished enantiomeric products of identical % ee.
(17) We found that a 2:1 ligand/copper ratio led to complete inhibition of the reaction.
(18) CCDC 268029 (4-bromoanilide of **2b**) and CCDC 268030 (**7**) contain the supplementary crystallographic data for this communication. These data can be obtained online free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21 EZ, U.K.; Fax (+44) 1223−336−033; or deposit@cccd.cam.ac.uk).
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