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Vol. 80 Commemorative Accounts

Stereoselective Conjugate Addition Reactions Using In Situ Metallated Terminal Alkynes and the Development of Novel Chiral P,N-Ligands

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In this account, new methods for the catalytic and stereoselective conjugate addition of terminal alkynes are described. Our laboratories have disclosed asymmetric addition reactions to aldehydes and imines using a combination of a zinc or copper salt and a terminal alkyne. Under these conditions, terminal alkyne is transformed in situ into an alkynyl metal species. Recently, it was found that these in situ generated alkynyl metal species can undergo conjugate additions to alkylidene malonate-type acceptors. In the zinc(II) triflate-catalyzed system, a highly diastereoselective conjugate addition has been realized using a chiral oxazepene acceptor. Subsequently, alternative conjugate addition protocols have been developed which employ a terminal alkyne, substoichiometric amounts of copper and a highly eletrophilic Meldrum's acid derived acceptor. This reaction can be made enantioselective using a novel atropisomeric P,N-ligand (PINAP). With this ligand, excellent enantioselectivities can be achieved for the conjugate addition of aromatic alkynes to various Meldrum's acid derived acceptors.

1. Introduction and Background

1.1 General Introduction. The conjugate addition of carbon nucleophiles is one of the most useful methods for C–C bond formation.[1] Recent progress in this field led to the discovery of catalytic asymmetric variants of this reaction allowing the access to various useful chiral building blocks.[2] Despite the remarkable achievements in this area, the conjugate addition of alkynyl nucleophiles has been very limited.[3] As part of the ongoing projects in the Carreira group, we have been focused on application of in situ generated metal alkynylides as nucleophiles for various synthetically useful reactions.[4] At the outset of our studies, there were only a handful of methods available that would allow stereoselective conjugate addition of preformed metal alkynylides. It has not been discovered until recently that metal alkynylides derived from zinc and copper can engage in stereoselective conjugate addition reactions.

In this introduction, some representative examples of conjugate addition reactions using different metal alkynylides are presented and these are organized by the metal employed. Also, recent developments of the enantioselective variants are briefly presented. The discussion of acceptors is focused on the reactivity of differently substituted α,β-unsaturated carbonyl compounds.

1.2 Metal Alkynylides. Terminal alkynes represent a special case amongst hydrocarbons, because they are exceptionally acidic compared to alkenes and alkanes (Fig. 1). The greater acidity of alkynes can be attributed to the higher s-character of the carbon atom due to its sp-hybridization.[5]

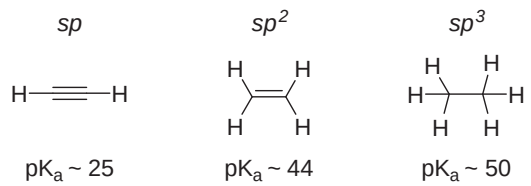
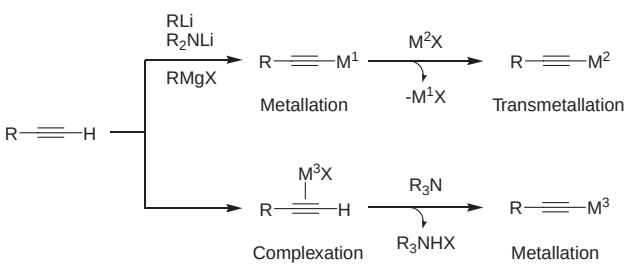


Fig. 1. Approximate acidities of C_2 hydrocarbons relative to water.[6,7]



Scheme 1.

Deprotonation of a terminal alkyne can be achieved with strong bases, such as organolithiums,[8] lithium amides,[9] or Grignard reagents[10] (Scheme 1). The metal alkynylides obtained can subsequently be subjected to transmetallation with other metals.[11] Alkali metal alkynylides are used extensively in organic synthesis, because they are excellent nucleophiles

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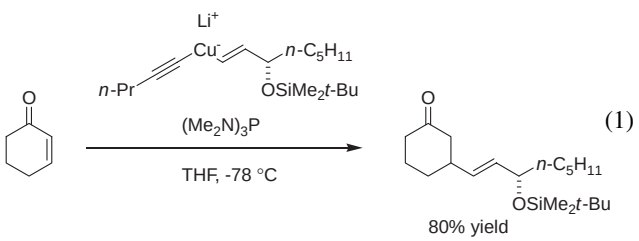
and add to a broad range of electrophiles including aldehydes, ketones, imines, and epoxides.[12]

Metal alkynylides can also be prepared using transition metals. A series of d-block elements that have a high affinity towards π-bonding to C–C triple bonds can acidify the terminal proton in such a way that it can be deprotonated by very mild bases such as tertiary amines ($pK_a \approx 11$). This has been shown to be case the for Ag^I, Au^I, Cu^I, Ir^I, Pd^{II}, Rh^I, Ru^{II}, and Zn^{II} amongst others.[13] In general, the alkynylides derived from these metals are much less nucleophilic than those derived from alkali metals with respect to addition reactions. The use of these metallated terminal alkynes in C–C bond-forming reactions is prevalent in organic synthesis.[9] Most notably, copper alkynylides are known to undergo cross-coupling reactions in the presence of palladium catalysts.[14]

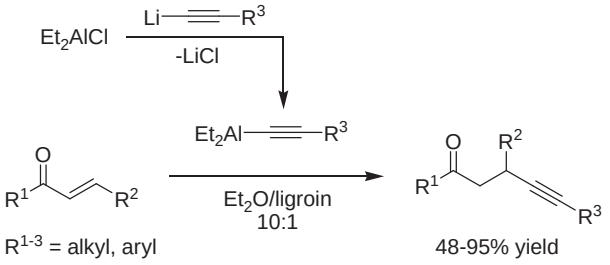
In 1999, our group reported a distinct method for the formation of zinc alkynylides under very mild and operationally simple conditions using $Zn(OTf)_2$ and an amine base at room temperature.[15,16] The alkynylides obtained under these conditions react in situ with a variety of electrophiles such as nitrones, aldehydes, ketones, and *N*-acylimminium ions.[4,17] The addition of such alkynylides to aldehydes can be performed in an asymmetric fashion in the presence of inexpensive *N*-methylephedrine.[18,19] This methodology has been applied in the context of several total syntheses of natural products (i.e. epothilone A and B,[20] epoxomicin,[21] gigantecin,[22] leucascandrolide A,[23] indolizidine,[24] and strongylodiol A and B).[25]

1.3 Conjugate Addition of Preformed Metal Alkynylides. As mentioned above, metal alkynylides are very useful reagents in 1,2-addition reactions to carbonyl compounds for preparation of propargyl alcohols and amines. However, the regio- and chemoselective 1,4-addition of terminal alkynes to α,β-unsaturated carbonyls has been a great challenge. Metal alkynylides derived from alkali metals undergo 1,2-addition preferentially. Moreover, the method most commonly used for regioselective addition of alkyl and alkenyl groups, namely the use of copper(I) reagents[26,27] has been thwarted by the inertness of copper(I)–alkynylides.[28] This has lead to the use of alkynes as dummy ligands in mixed organocuprates to ensure the selective transfer of more reactive groups (Eq. 1).[29] Over the past several decades, this research area has been addressed by many synthetic chemists. Most successes have been achieved using boron and aluminium alkynylides.



(1)

1.3.1 Conjugate Addition of Aluminum Alkynylides: The first report of a conjugate addition of an alkyne was published in 1971 by Hooz and Layton.[30] In analogy to the Nagata hydrocyanation reaction which employs Et_2AlCN for a regioselective 1,4-addition of cyanide to enones,[31] preformed aluminum alkynylides $Et_2AlC{\equiv}CR$ (prepared by transmetallation of the lithiated alkynes to diethylaluminum chloride) underwent conjugate addition to α,β-unsaturated ketones. The products were obtained at room temperature in a mixture of ligroin/diethyl ether in 30–95% yield. (Scheme 2).



Scheme 2.

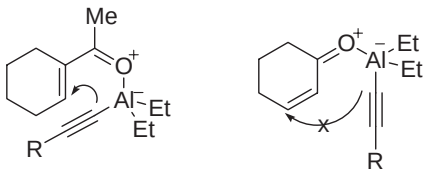
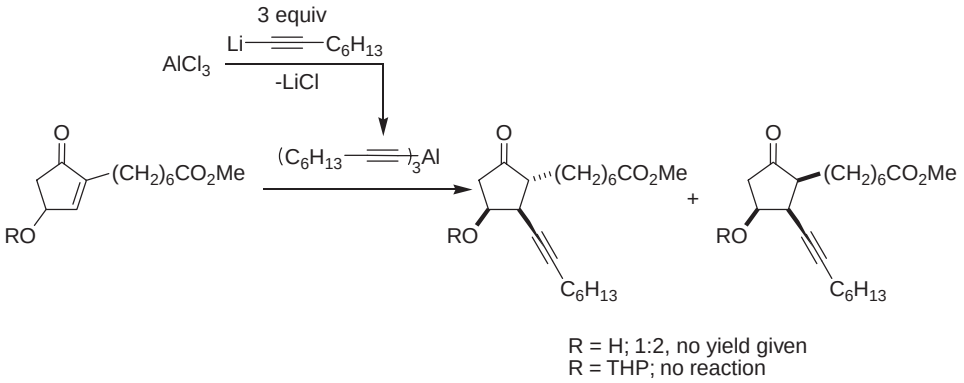


Fig. 2. Proposed transition state for the conjugate addition of aluminum alkynylides.

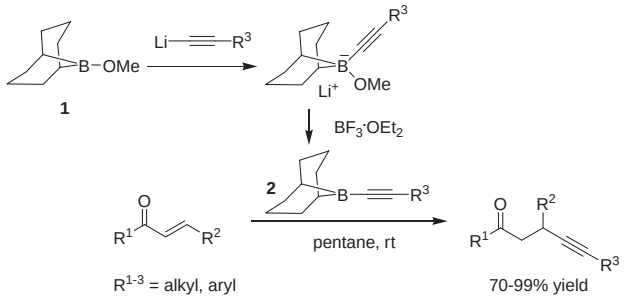
Interestingly, only ketones that can adopt an *s-cis* conformation participated in conjugate addition, whereas cyclic α,β-unsaturated ketones that are locked in the *s-trans* conformation underwent 1,2-addition preferentially. These observations lead the authors to suggest a 6-membered transition state, where the aluminum activates the enone by coordination to the carbonyl oxygen (Fig. 2). In the case of enones which can adopt an *s-cis* conformation, optimal alignment for 1,4-addition is possible. In contrast, cyclic enones such as cyclohexenone afford only 1,2-addition adducts because of a geometrical constraints. However, it was found that conjugate addition of aluminum alkynylides to enones that are locked in the *s-trans* conformation can be achieved using an in situ formed nickel(I) catalyst from $Ni(acac)_2$ and DIBAL-H.[32]

Shortly thereafter Pappo and Collins reported that trialkynylaluminum reagents prepared from $AlCl_3$ and three equivalents of lithium alkynylide add to γ-hydroxycyclopentenones affording 1,4-addition adducts as a mixture of diastereomers (Scheme 3).[33] The attack of the alkyne occurs *syn* to the free hydroxy group, suggesting its role as a directing group. This is in agreement with a control experiment, in which the corresponding *O*-THP-protected γ-hydroxycyclopentenone did not react with the trialkynylaluminum reagent.

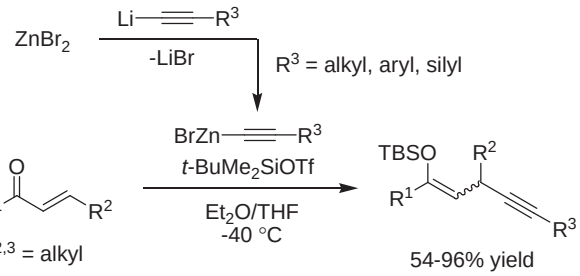
1.3.2 Conjugate Addition of Boron Alkynylides: Pappo and Collins reported for the first time that trialkynylboron reagents can be employed for the conjugate addition of alkyne nucleophiles to a cyclic enone.[33] A more synthetically useful method was subsequently described by Brown et al. (Scheme 4).[34] Treatment of *B*-MeO-9-BBN with a lithium alkynylide affords the intermediate ate-complex, which is converted into the reactive alkynylide **7** upon addition of BF_3 etherate. These *B*-1-alkynyl-9-BBN reagents add to enones in pentane at room temperature regioselectively furnishing products in 70–99% yield. However, this method proceeds with enones that can adopt an *s-cis* conformation; enones that are



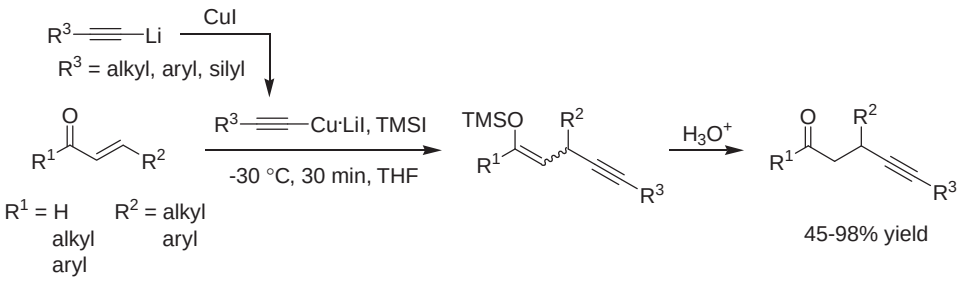
Scheme 3.



Scheme 4.



Scheme 6.



Scheme 5.

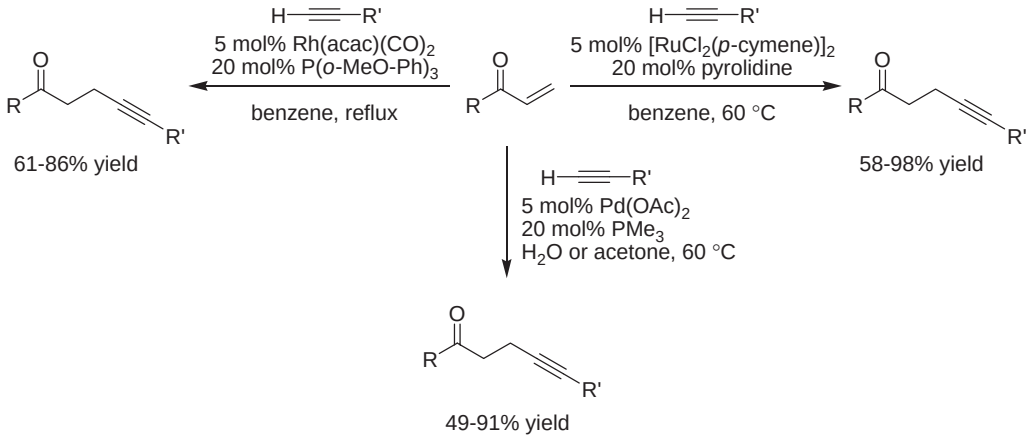
locked in the *s-trans* conformation do not react. The authors provided the same explanation as in the case of aluminum alkynylides, namely the reaction is believed to proceed via a 6-membered transition state (analogous to Fig. 2), requiring the appropriate disposition of C=O and C=C bonds.

1.3.3 Conjugate Addition of Copper and Zinc Alkynylides: Copper alkynylides are generally too unreactive to participate in conjugate additions, which has been attributed to the π-back bonding of Cu^{I} to alkynes.[35] However, it has been demonstrated, that by additional activation of electrophiles with silylating reagents[36] 1,4-addition can take place.[37] The transmetallation of lithium alkynylide to CuI at $-78\,^{\circ}C$ was followed by addition of Me_3SiI. Under these conditions, copper alkynylides undergo conjugate addition to enones and enals in THF at $-30\,^{\circ}C$ to provide the silylenolethers. Hydrolysis during the aqueous workup furnished the β-alkynyl carbonyl products in 45–98% yield (Scheme 5).[38] A related protocol was reported which utilizes *t*-$BuMe_2SiOTf$, and the conjugate addition of copper alkynylides to enones could be effected.[39] In this case the more stable TBS–enol ether products can be isolated after the conjugate addition in 64–93% yield.

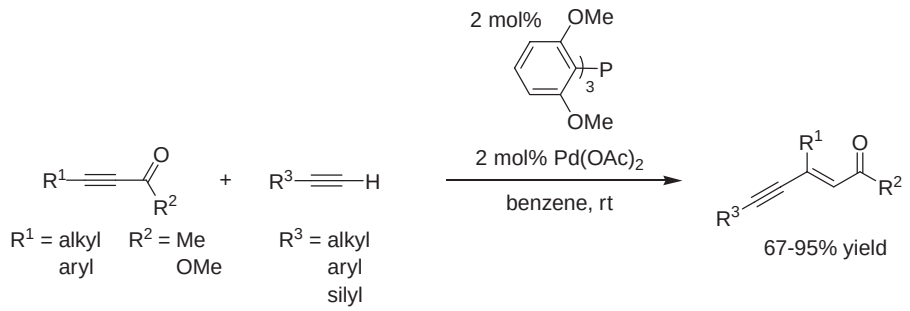
The conjugate addition of zinc alkynylides to enones was also enabled by the addition of electrophilic silylating reagents. Lithiated alkynes were transmetallated to $ZnBr_2$ and thus formed RC≡CZnBr was added to a mixture of *t*-$BuMe_2SiOTf$ and an enone (Scheme 6). The TBS–enol ethers were obtained as mixtures of *E* and *Z* isomers in 54–96% combined yield.[40]

1.3.4 Conjugate Addition of Alkynes Involving Palladium-, Rhodium-, and Ruthenium-Catalysis: More recently, there have been reports of transition-metal-catalyzed conjugate additions of terminal alkynes using palladium(II)-,[41] rhodium(I)-,[42] and ruthenium(II)-catalysts[43,44] (Scheme 7). A wide range of alkynes participate in 1,4-additions using only 5 mol % of suitable metal complexes at elevated temperatures. However, these methods are strictly limited to β-unsubstituted vinyl ketones or acrylates as acceptors.

It was shown by Trost and co-workers that Pd^{II} can catalyze a dimerization reaction of terminal alkynes to give enynes.[45] The authors further explored this process and demonstrated



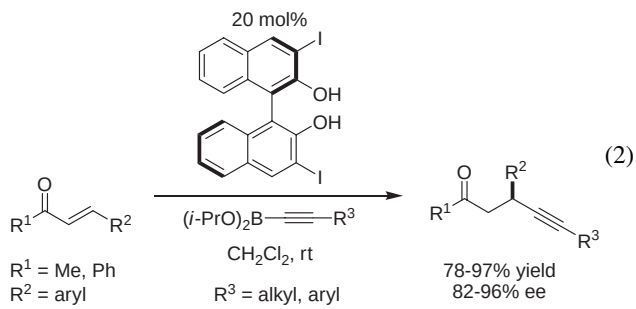
Scheme 7.



Scheme 8.

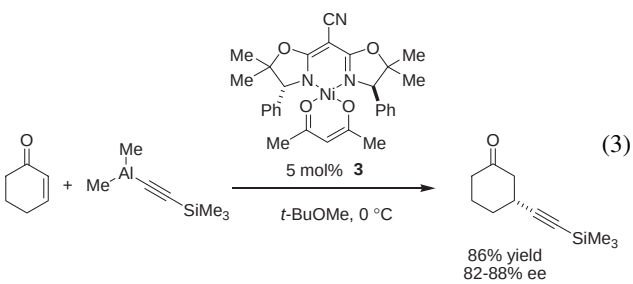
that in the presence of acceptor alkynes, such as aryl and alkyl propiolates, terminal alkynes preferentially participate in conjugate addition reactions (Scheme 8). The use of the electron rich tris(2,6-dimethoxyphenyl)phosphine is critical for the reaction. In the presence of 2 mol % $Pd(OAc)_2$ and the phosphine a variety of terminal alkynes underwent conjugate addition to acceptor alkynes in benzene at room temperature furnishing the *trans*-enynes exclusively in 67–95% yield.

1.4 Enantioselective Conjugate Addition of Terminal Alkynes. There had been few examples of enantioselective conjugate addition of alkynes until recently. Building upon the work of Pappo and Brown, Chong et al. had reported that preformed alkynyl boronates derived from 3,3′-diphenyl-BINOL participate in conjugate addition to aryl-enones in 81–99% yield and 16–98% enantiomeric excess.[46] The authors published an improved process that allowed the use of 3,3′-diiodo-BINOL in 20 mol % loading to catalyze the addition of alkynyl boronates to aryl-enones, providing the products in 78–97% yield and 82–96% ee (Eq. 2).[47]



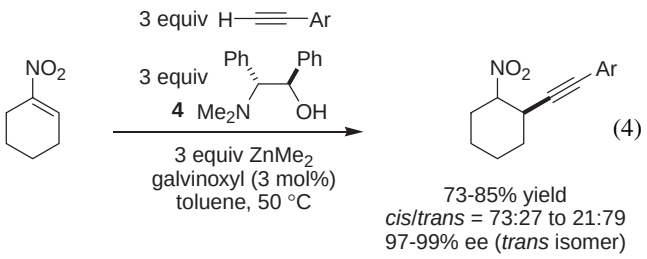
(2)

Another catalytic enantioselective conjugate addition of terminal alkyne was reported by Corey and Kwak. In the presence of chiral nickel–bisoxazoline complex, almunium alkynylides undergo stereoselective conjugate addition to cyclohexenone.[48] The addition of TMS–acetylene to cyclohexenone using 5 mol % of bisoxazoline–nickel catalyst **3** furnished the product in 86% yield and 82–88% ee (Eq. 3). Interestingly, the use of a nickel(II) catalyst proved essential for turnover; the corresponding Ni^{I} species obtained after reduction with DIBAL-H, afforded the product in comparable enantioselectivity, but the complex had to be used in stoichiometric amounts.



(3)

Very recently, a new zinc-mediated enantioselective conjugate addition was reported by Tomioka et al.[49] The addition of aryl alkynes to nitro olefins was accomplished using $ZnMe_2$ and the chiral amino alcohol **4**. The products were obtained in 73–85% yield and 97–99% enantiomeric excess as mixtures of *cis* and *trans* isomers (Eq. 4). In this case, the addition of galvinoxyl as a radical scavenger was essential to obtain the products in high yields.[50]



The authors proposed a model on the basis of the mechanistic work by Noyori, Oguni, and co-workers on the β-amino alcohol-catalyzed addition of dialkylzinc reagents to aldehydes,[51] which rationalizes the absolute configuration of the newly formed stereogenic center (Fig. 3). A bimetallic zinc complex serves as a Lewis acid, that activates the nitroalkene by coordination of one zinc atom to the oxygen of the nitro group, subsequently the zinc alkynylide is delivered from the second zinc to provide the product.

1.5 Meldrum's Acid Derived Acceptors. Differently substituted acceptors display diverse reactivities in conjugate addition reactions. Typically, acceptors for conjugate additions consist of a C–C double or triple bond attached to at least one π-acceptor (i.e. carbonyl, cyano, nitro, sulfinyl, or sulfonyl group), that activates the β-position for nucleophilic addition. As a guideline for the prediction of the reactivity of different acceptors one can compare the stability of the enolate formed after addition. Thus, the lower the pK_a of the corresponding C_α proton, the more reactive the corresponding acceptor (Fig. 4).

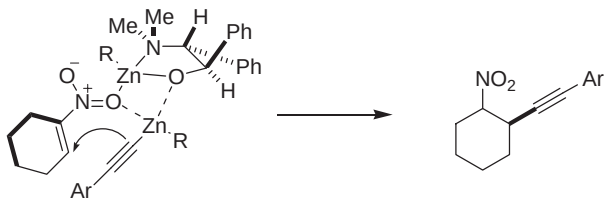


Fig. 3. Proposed model to explain of the sense of asymmetric induction.[49]

During the course of our studies, cyclic acceptors possessing two carbonyl functionality such as those derived from Meldrum's acid (**5**) have been identified as very useful and versatile reagents for the conjugate addition of relatively unreactive metal alkynylides. The eponymous acid **5** was first synthesized by Meldrum in 1908 from malonic acid and acetone in acetic anhydride and sulfuric acid.[54] Its structure was initially misassigned to be β,β-dimethyl-β-propiolactone-α-carboxylic acid (**6**), and corrected only 40 years later.[55] It is exceptionally acidic compared to barbituric acid, dimedone, and dimethyl malonate (Fig. 5). This phenomenon is conventionally referred to as an anomaly, but was recently rationalized in a computational study.[52b] Calculations showed a correlation between the energy of the reactive hybrid orbital (RHO) and the experimental standard ionization energy. The major component of the unoccupied RHO is the σ^*_{CH} orbital with a contribution of the adjacent carbonyl π^* orbital; upon deprotonation electron density is transferred form the base lone pair into the antibonding σ^*_{CH} leading to C–H bond cleavage.

Meldrum's acid is used extensively in synthetic organic chemistry.[56] The products obtained after Knoevenagel condensation with aldehydes are very reactive acceptors for conjugate additions (Scheme 9). The condensation can be per-

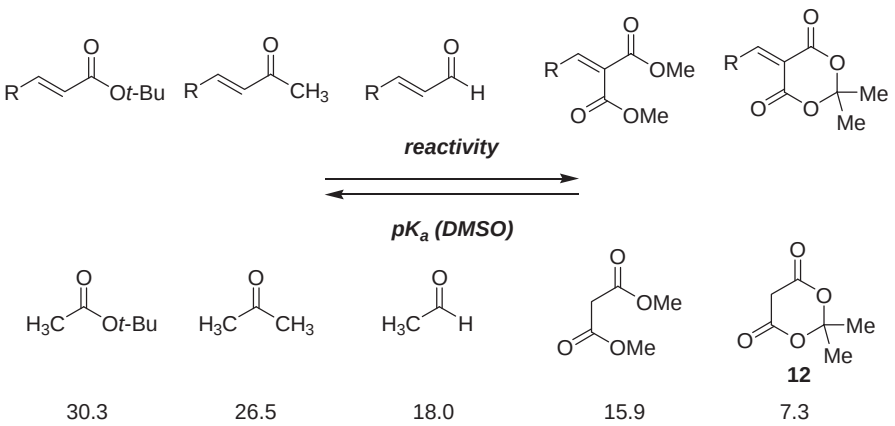


Fig. 4. Trends in the reactivity of acceptors.[52,53]

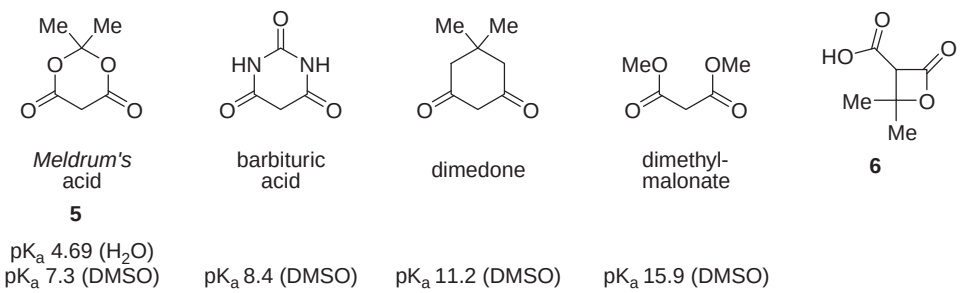
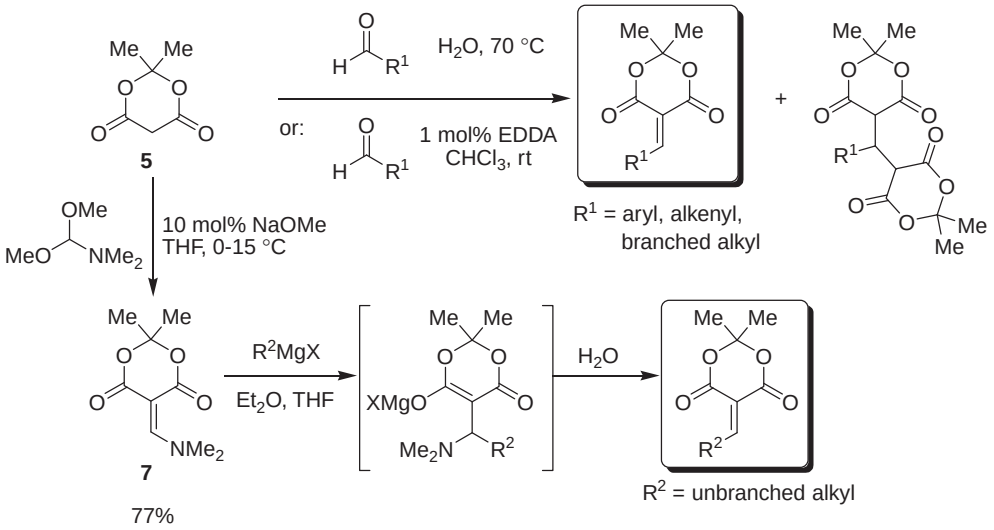
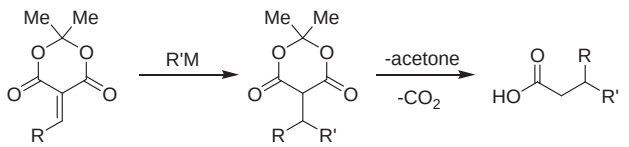


Fig. 5. Acidity of Meldrum's acid and related compounds.[52]



Scheme 9.



Scheme 10.

formed using an ammonium salt catalyst, for example EDDA (ethylenediammonium diacetate),[57] or simply by heating the components in water.[58] A minor byproduct, which can be conveniently removed by crystallization, results from conjugate addition of a second equivalent of Meldrum's acid (**5**). Alternatively, the acceptors derived from aliphatic aldehydes can be prepared by the addition of Grignard regents to **7**, which can be obtained by condensation of Meldrum's acid with dimethylformamide dimethylacetal.[59] The magnesium enolate formed after addition collapses only upon aqueous workup, preventing the double addition.

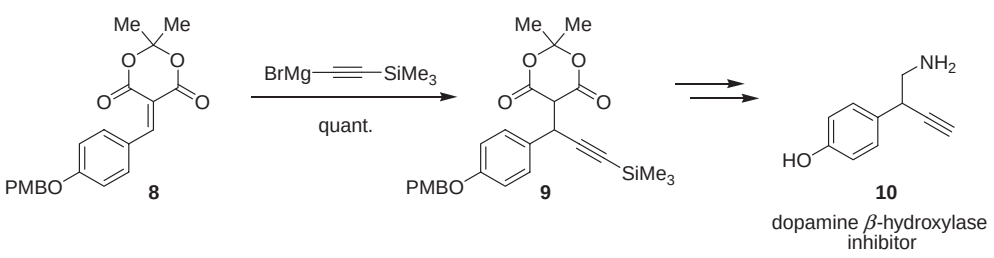
The conjugate addition of organometallic reagents to Meldrum's acid derived acceptors has been reported (Scheme 10). These include Grignard reagents,[60] organolithium compounds[61] as well as dialkylaluminum chlorides.[62] The products obtained are versatile building blocks that can be converted into a variety of compound classes, as exemplified by the decarboxylation to the corresponding carboxylic acid (Scheme 10).[56] Our group has developed a method for enantioselective conjugate addition of diethylzinc to these acceptors so as to read using copper–phosphoramidite complex.[63] More recently, Fillion and co-workers described the use of 5-(1-arylethylidene) Meldrum's acid as a substrate for enantioselective conjugate addition of dialkylzinc reagents, and this reaction can generate quaternary stereogenic center in high enantioselectivities using a chiral copper–phosphoramidite catalyst.[64]

There have been several reports of conjugate additions of metal alkynylides to Meldrum's acid derived acceptors in the literature, notably in the context of the synthesis of pharmacologically relevant molecules. Addition of trimethylsilylethynyl magnesium bromide to acceptor **8** provided the product **9** in quantitative yield (Scheme 11). The adduct was further elaborated into the dopamine β-hydroxylase (DBH) inhibitor **10**.[65]

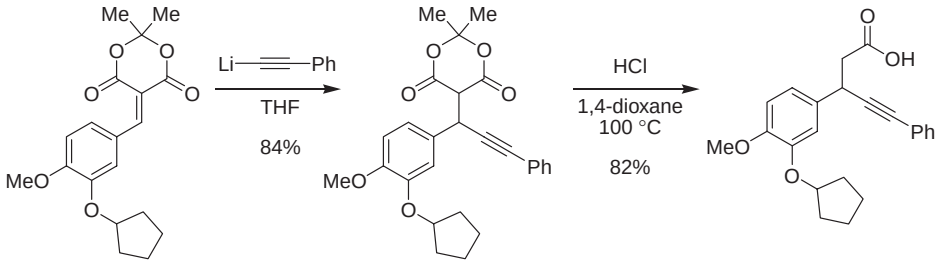
Lithium phenylalkynylide underwent conjugate addition to acceptor **11** (Scheme 12) and the adduct **12** was decarboxylated to give tumor necrosis factor (TNF) inhibitor **13**.[66] Subsequent Curtius rearrangement provides access to gastin-releasing peptide (GRP) receptor antagonists.

A chiral acceptor for diastereoselective conjugate addition of organometallic reagents was developed by Mukaiyama et al.[67] Stepwise condensation of ephedrine with malonic acid provided the chiral oxazepane dione **14** (Scheme 13). Condensation with aldehydes under conditions reported by Lehnert[68] provided a mixture of *Z* and *E* isomers **15** and **16** in a ratio ranging from 15:85 to 1:99.[69]

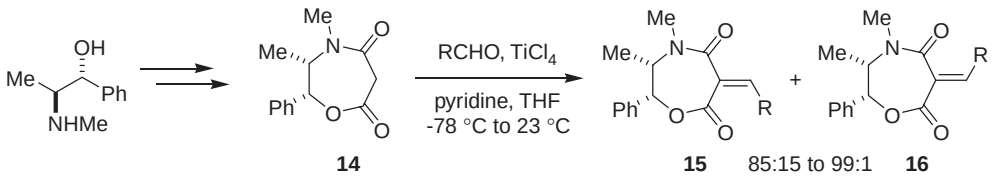
Conjugate additions of Grignard reagents (alkyl and aryl but no alkynyl groups were examined) to **15** was found to be highly diastereoselective when they were carried out at $-78\,^{\circ}C$ in the presence of catalytic amounts of $NiCl_2$ (Scheme 14). The attack occurs *syn* to the residues on the oxazepane ring.[70] The adducts are treated with aqueous acid at elevated temperature



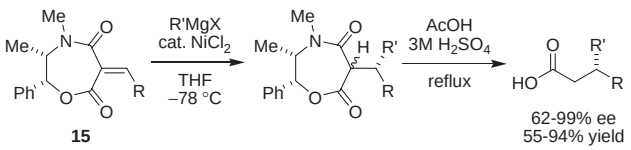
Scheme 11.



Scheme 12.



Scheme 13.



Scheme 14.

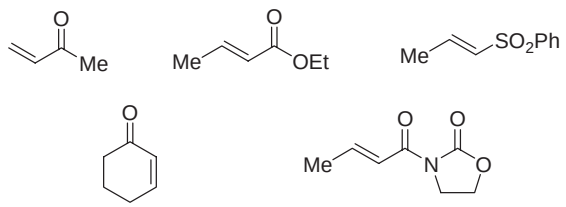
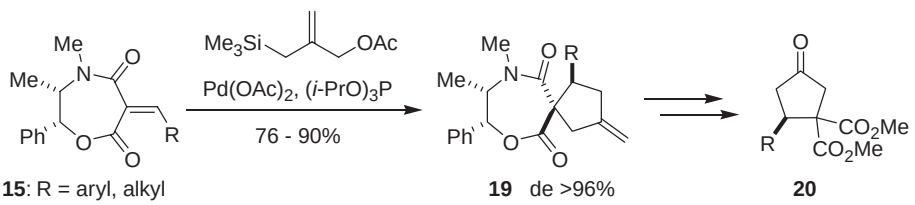


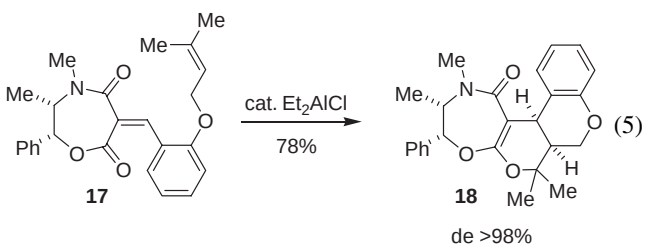
Fig. 6. Michael acceptors not suitable for the conjugate addition of zinc–alkynylides.



Scheme 15.

to provide the corresponding carboxylic acids in 55–94% yield and 62–99% ee.

The oxazepane dione acceptors were also used in two other synthetically useful processes. Tietze et al. showed that oxazepane **17** can participate in a highly diastereoselective, aluminum-catalyzed hetero Diels–Alder reaction (Eq. 5).[71] The product **18** was obtained in >98% diastereomeric excess with the facial selectivity being the same as in the conjugate addition reaction.[72]



(5)

A palladium-catalyzed diastereoselective trimethylenemethane cycloaddition with **15** was reported by Trost et al. (Scheme 15).[73] The cyclopentane **19** was obtained in 84% yield and >96% diastereomeric excess. Subsequent removal of the auxiliary allowed elaboration into cyclopentanone **20**.

2. Conjugate Addition of In Situ Generated Zinc Alkynylides[74]

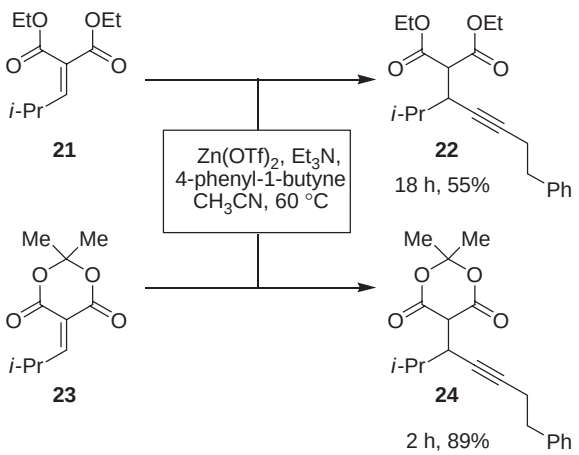
2.1 Conjugate Addition to Meldrum's Acid Derived Acceptors. As a part of the project in the Carreira group aimed at identifying new electrophiles for the zinc alkynylides formed in situ by $Zn(OTf)_2$ and an amine base, we have screened different types of acceptors as potential candidates. The study revealed that alkenes bearing only one acceptor group (Fig. 6) were not sufficiently electrophilic for the addition of the in situ generated zinc alkynylide.

However, more electron deficient *gem*-diactivated alkenes proved to be suitable substrates (Scheme 16). As a lead result,

the reaction of alkylidene malonate **21** with 4-phenyl-1-butyne, $Zn(OTf)_2$ and triethylamine in acetonitrile at 60 °C, the product **22** was obtained in 55% yield after 18 h, along with recovered starting material. Under identical conditions, the reaction achieved full conversion after 2 h when acceptor **23**, derived from Meldrum's acid (**5**), was used. After purification, **24** was isolated in 89% yield.

Under the optimized conditions, the in situ generated zinc alkynylides add to various Meldrum's acid derived acceptors to form adducts **25**–**29** in 85–90% isolated yield (Fig. 7). The method allows the addition of different alkynes including alkyl-, aryl-, and silyl-substituted alkynylides to the Meldrum's acid derived acceptors. This protocol with Zn^{II} is achieved both the ease of execution and short reaction times. It represents the first general methodology for the addition of unactivated teminal alkynes to Meldrum's acid derived acceptors.

Further studies aimed at the development of a catalytic asymmetric protocol revealed that the process necessitates stoichiometric quantities of $Zn(OTf)_2$. This is due to the formation of an insoluble zinc–enolate during the course of the reaction, which prevents turnover of zinc.[75] The use of chiral ligands such as *N*-methylephedrine led to a deceleration of the reaction rate. Moreover, the products were formed in trace amounts and without asymmetric induction. This result contrasts the reaction of the in situ prepared zinc alkynylides with aldehydes, where the reaction is significantly accelerated in the presence of aminoalcohol ligands. We turned our attention to investigate a diastereoselective version of this promising reaction, that would allow the preparation enantiomerically enriched β-alkynyl acids.



Scheme 16.

2.2 Diastereoselective Conjugate Addition of Zinc Alkynylides. Chiral oxazepanedione acceptors **15** would be a convenient and useful reaction partners leading to optically active β-alkynyl acids provided they would be sufficiently electrophilic toward the in situ generated alkynylzinc reagent. The oxazepanedione **14** was accessed in a three-step sequence without purification of the intermediates (Scheme 17). Heating of (−)-ephedrine and dimethylmalonate in MeOH was followed by treatment with LiOH.[76] The unpurified monoacid was cyclized with Mukaiyama's reagent[67] providing **14** in 46% yield over three steps. Condensation of **14** with aldehydes was mediated by $TiCl_4$ and pyridine[68] and gave predominantly the (*Z*)-alkylidene products (6–11:1, 72–97% yield).[77] Importantly, the minor (*E*)-isomers could be conveniently removed by chromatography on silica gel.

Gratifyingly, the addition of zinc alkynylides to oxazepanedione acceptors proceeded smoothly to completion at 23 °C in CH_2Cl_2. Optimal results were obtained using 60 mol % of $Zn(OTf)_2$ and the conjugate addition adducts are obtained in 63–95% yield as a mixture of diastereomers (Fig. 8). The diastereomeric products result from the C_α stereogenic center produced upon protonation of the enolate, and this stereogenic center is prone to epimerization under these conditions. Therefore, the stereoselectivity at C_β was analyzed after converting the conjugate addition adducts into the corresponding β-alky-

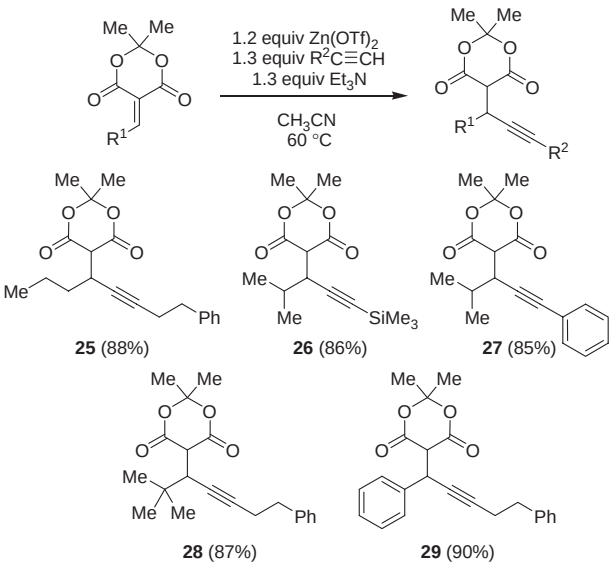
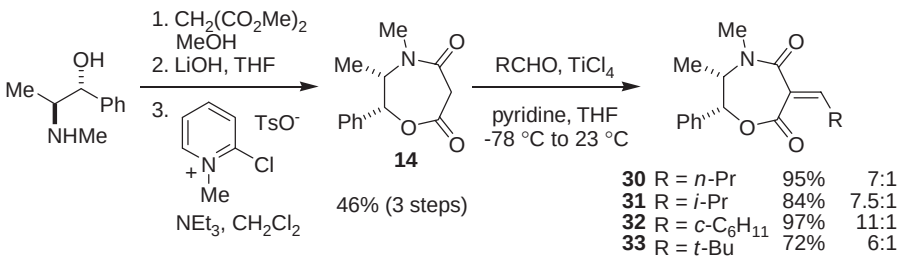


Fig. 7. Conjugate addition of zinc–alkynylides to Meldrum's acid derived acceptors.



Scheme 17.

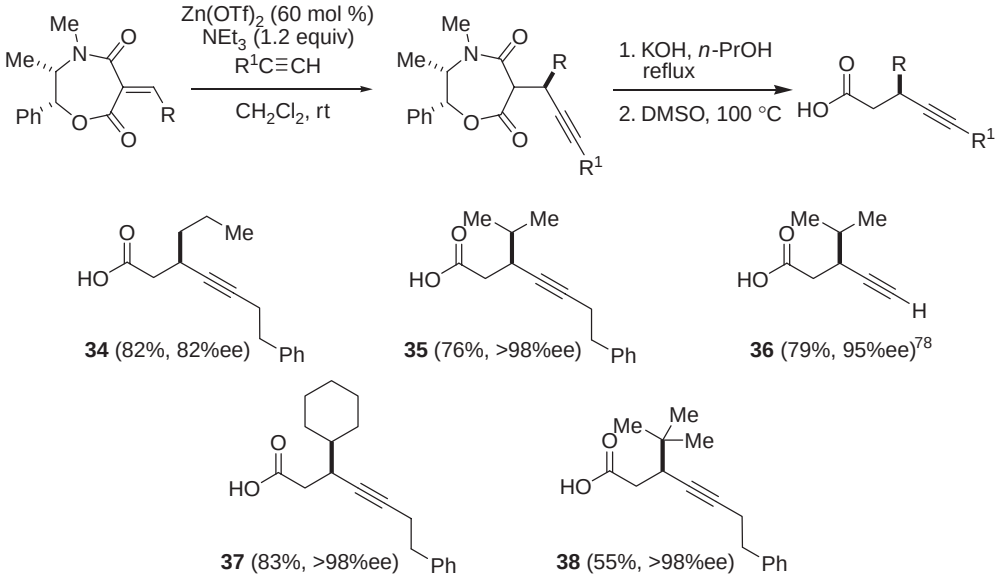
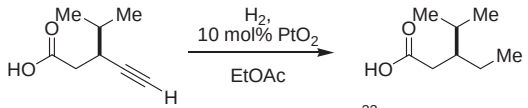


Fig. 8. Diastereoselective addition of zinc alkynylides to oxazepanedione acceptors.

nyl acids **34**–**38** and their enantiomeric excess were determined by chiral HPLC. The alkaline hydrolysis of the chiral auxiliary can be convineiently carried out with KOH in *n*-propanol leading to the intermediate diacids, and these malonic acid derivatives were decarboxylated in DMSO at 100 °C producing **34**–**38** in 84–92% yield.[78]

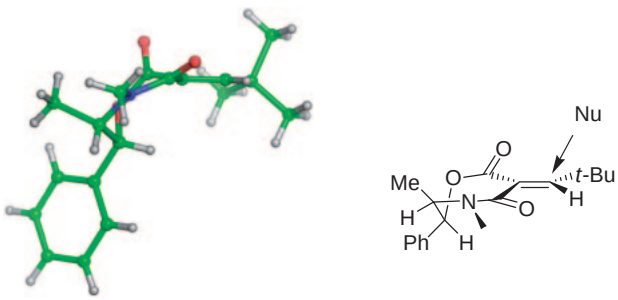
The conjugate addition is highly diastereoselective for acceptors with branched substituents (95–98% ee). For sterically less bulky substrates, the enantioselectivity was slightly attenuated (R = *n*-Pr, Fig. 8). The acceptors bearing aromatic or alkenyl groups were unreactive under these conditions. In contrast to the previous studies involving the addition of alkyl Grignard reagents to these acceptors, the conjugate addition of in situ generated zinc alkynylides exhibited high diatereoselectivities even at higher temperatures.[67] Importantly, when the reaction was conducted at 60 °C, the loading of Zn^{II} could be reduced to only 20 mol %.[74]

The absolute configuration of **36** was determined by chemical correlation after conversion to 3-ethyl-4-methylpentanoic acid (Eq. 6). Hydrogenation of **36** using 10 mol % PtO_2 in ethyl acetate furnished the alkane in 97% yield. Comparison of the sign of the optical rotation with the value reported in the literature confirmed the absolute configuration of **36** to be *S*.[79] The stereoselectivity of the addition is consistent with attack of the zinc–alkynylides *syn* to the substituents on the oxazepane ring and this result is in agreement with all the studies that involve nucleophilic addition to these oxazepane acceptors (Fig. 9).[71]



(6)

Two different acceptors were studied in the context of conjugate addition of in situ generated zinc alkynylides. The conjugate addition to Meldrum's acid derived acceptors proceeded



X-ray structure of **33**

Fig. 9. Explanation of the diastereoselectivity in the zinc-catalyzed addition of alkynes to oxazepanedione acceptors.

smoothly to afford the 1,4-addition adduct in excellent yields. The attempts to make this process catalytic or enantioselective by addition of chiral ligands were not successful. However, the reactions with chiral oxazepane derived acceptors can provide access to enantiomerically enriched β-alkynyl carboxylic acids in high selectivities.

3. Conjugate Addition of In Situ Generated Copper Alkynylides to Meldrum's Acid Derived Acceptors[80]

3.1 Development of a Catalytic Protocol. The acceptor derived from Meldrum's acid was identified as very reactive and useful reaction partner in the conjugate addition of the zinc alkynylides. Although unreactive nature of alkynyl copper reagents is well precedented, we speculated that extraordinary electrophilicity of the Meldrum's derived acceptors may enable conjugate addition of copper alkynylides.

Alkynyl copper(I) species are readily obtained by combining terminal acetylenes with copper(I) salts in the presense of a base, and their preparation can even be carried out in water.[81] However, this procedure requires exclusion of oxygen because copper(I) alkynylides can potentially undergo oxida-

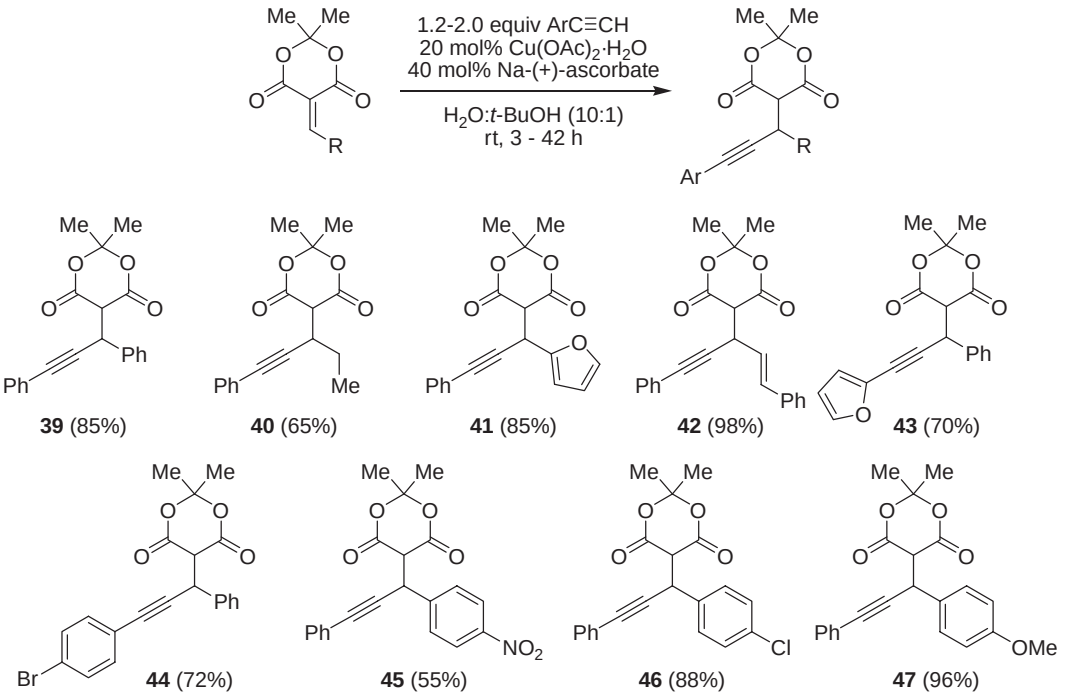
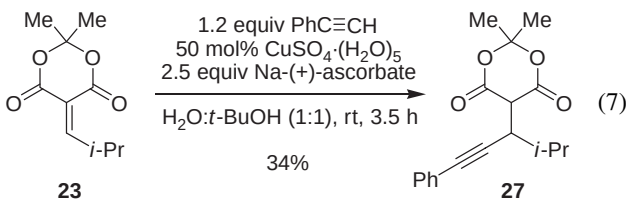


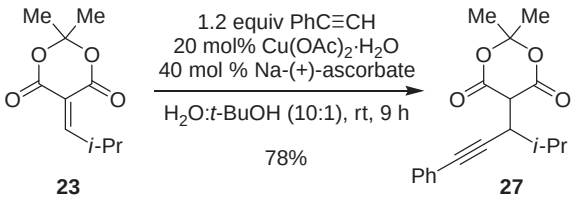
Fig. 10. Conjugate addition of terminal alkynes to Meldrum's acid derived acceptors.

tive Glaser coupling.[82] Alternatively copper(I)–alkynyl reagents are conveniently prepared from copper(II) salts in combination with a reductant such as sodium ascorbate.[83,84] This procedure would allow facile generation of copper(I)–alkynylides by avoiding the handling of copper(I) salts which can be readily oxidized. But more importantly, we anticipated that the presence of reducing agent may preclude oxidative acetylide coupling. In our preliminary experiments, we chose the conditions using 1:1 H_2O:*t*-BuOH as the solvent mixture and using $CuSO_4$ pentahydrate and excess of sodium ascorbate as the Cu^I source. We were pleased to find that phenylacetylene underwent conjugate addition to acceptor **23** to give the adduct **27** in 34% yield along with 28% recovered starting material (Eq. 7).



(7)

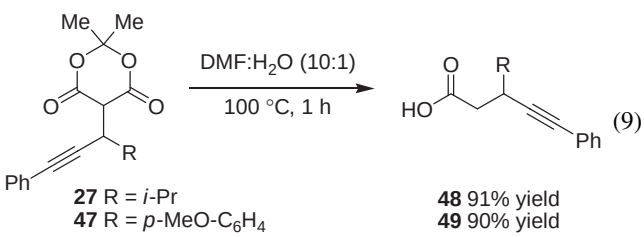
In the following reaction optimization studies, higher yields were achieved using lower loadings of Cu^{II} and sodium ascorbate as well as changing the solvent ratio. A survey of various copper(II) salts showed that copper(II) acetate monohydrate gives the highest yield (Eq. 8). It was found that the reaction does not proceed in the absence of either ascorbate or copper(II) salts (or both). Surprisingly, rigorous exclusion of oxygen from the reagents and solvents resulted in the inhibition of the conjugate addition. Also the conjugate addition only occurs in the presence of water and the addition of organic cosolvents significantly reduced the reaction rate. There was no stereoinduction from the ascorbate in this process, and these conjugate addition adducts are obtained as racemic mixtures.



(8)

With the optimized conditions established, a number of differently substituted substrates were reacted with aryl acetylenes (Fig. 10). A variety of acceptors bearing aromatic, heteroaromatic, branched and unbranched aliphatic, as well as alkenyl groups gave the conjugate addition products in modest to excellent yields. Interestingly, in the case of $\alpha,\beta,\gamma,\delta$-diene acceptor, only 1,4-addition product was obtained (**42**, Fig. 10).[64b] Different aryl alkynes including heteroaromatics can be used as nucleophiles. However, the use of aliphatic alkynes such as 4-phenyl-1-butyne yielded the corresponding conjugate addition adduct only in 5–20% yields.

This process allows ready preparation of various β-alkynyl carboxylic acids. For example, the removal of the acetonide moiety and decarboxylation of **27** and **47** are accomplished by simply heating the solution in DMF/H_2O (10:1) and alkynyl acids **48** and **49** are obtained in 91 and 90% yield, respectively (Eq. 9).



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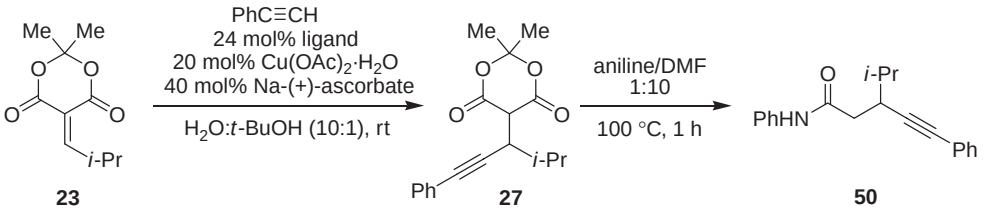


Scheme 18.

3.2 Development of a Catalytic Asymmetric Protocol. With this newly found process in hand we intended to develop an asymmetric version by adding chiral ligands for copper. Using the addition of phenylacetylene to **23** as the test reaction, a large number of ligands were screened with respect to the yield and enantiomeric excess of **27**. The enantiomeric excess was measured by chiral analytical HPLC after conversion of the adduct to the corresponding anilide **50** by heating in aniline/DMF 1:10 (Scheme 18).

The ligand survey included C_2-symmetric and non C_2-symmetric diphosphines; (pyridinyl)bisoxazolines; phosphoramidites; monophosphines, as well as (P,S)-; (S,N)-; (N,O)-; (S,N)-; (S,O)- and various (P,N)-ligands (Fig. 11). One ligand was superior to all the others: QUINAP furnished the product **27** in full conversion after 6 h at room temperature with an enantiomeric excess of 42%.

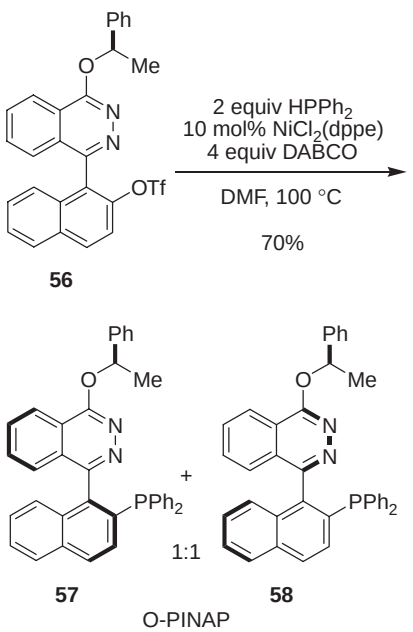
Because QUINAP was the only ligand leading to useful asymmetric induction in the copper-catalyzed conjugate alkyne addition to Meldrum's acid derived acceptors, we decided to use its scaffold as the basis for our further development of a more active and selective. Although QUINAP is commercially available, it is rather expensive. Its synthesis can be accomplished by a six-step sequence. However, the optical resolution of QUINAP must employ an expensive chiral palladium amine complex. Moreover, it was known that structural modifications on this ligand are not well tolerated, leading to problems in the resolution of enantiomers or lowering of the rotation barrier about the biaryl linkage resulting in racemization at room temperature. Therefore, we decided to develop a new ligand class, based upon the skeleton of QUINAP.

3.3 The Development of PINAP Ligands.[85] The ligand for our study must meet the following criteria: (1) The ligand has to be accessible in short sequence from inexpensive starting materials, that would allow access sufficient quantities for a thorough investigation of the reaction conditions; (2) The separation of the atropisomers has to avoid the use of palladium amine complexes in the resolution; (3) The ligand synthesis should be modular in order to accommodate structural modification. On the basis of these considerations, we developed the strategy delineated in Fig. 12. The use of 1,4-dichlorophthalazine as the core structure allows both the convenient construction of the biaryl unit[86] and subsequent introduction of a chiral controlling group. The introduction of an extra stereogenic center facilitates the separation of atropisomers by forming diastereomers. We termed the ligand PINAP for **P**hthalaz**I**ne**NAP**hthalene in analogy to QUINAP.

3.3.1 Synthesis of the PINAP Ligands: 1,4-Dichlorophthalazine (**52**) can be readily prepared in >100 g batches using a protocol reported by Sharpless et al.[87] Phthalhydrazide (**51**) was treated with PCl_5 at 140 °C. After distillative removal of $POCl_3$ and recrystallization, **52** was obtained in 67% yield on a 150 g (0.93 mol) scale (Scheme 19).[88] Susequently, it was coupled to 2-naphthol with aluminum chloride in dichloroethane at 80 °C.[89] The pure product was obtained by a simple filtration after aqueous workup in 86% yield on 63 g (0.3 mol) scale. This biaryl compound served as a common intermediate for the different ligands. To facilitate separation of the atropisomers, **53** was reacted with chiral alcohols and amines for subsequent evaluation.

Naphthol **53** was added to a mixture of NaH (2 equiv) and (*R*)-phenylethanol in THF at 23 °C (Scheme 20) to afford the diastereomeric aryl ethers **54** and **55** in 83% yield (dr 1:1). At this stage the two diastereomers obtained are easily separable by crystallization. The (*R*,*M*)[90] isomer **54** readily crystallizes selectively from Et_2O or CH_2Cl_2 (Fig. 13). However, we found that the biaryl moiety undergoes epimerization in the subsequent phosphination reaction at 100 °C (Eq. 10), therefore the separation of diastereomers should be carried out after the phosphination. Both of the diastereomers were converted into the corresponding triflate **56** with triflic anhydride and pyridine in CH_2Cl_2 at 0 °C in 91% yield.

The nickel-catalyzed coupling of **56** with $HPPh_2$ in DMF at 100 °C[91] furnished ligands **57** and **58** in 70% combined yield (Eq. 10). We refer to **57** and **58** as *O*-PINAP. The two atropisomeric diastereomers are separated at this stage either by chromatography on silica gel or, alternatively, by crystallization. The relative configuration of **57** was established as *R*,*P* by X-ray analysis (Fig. 14).



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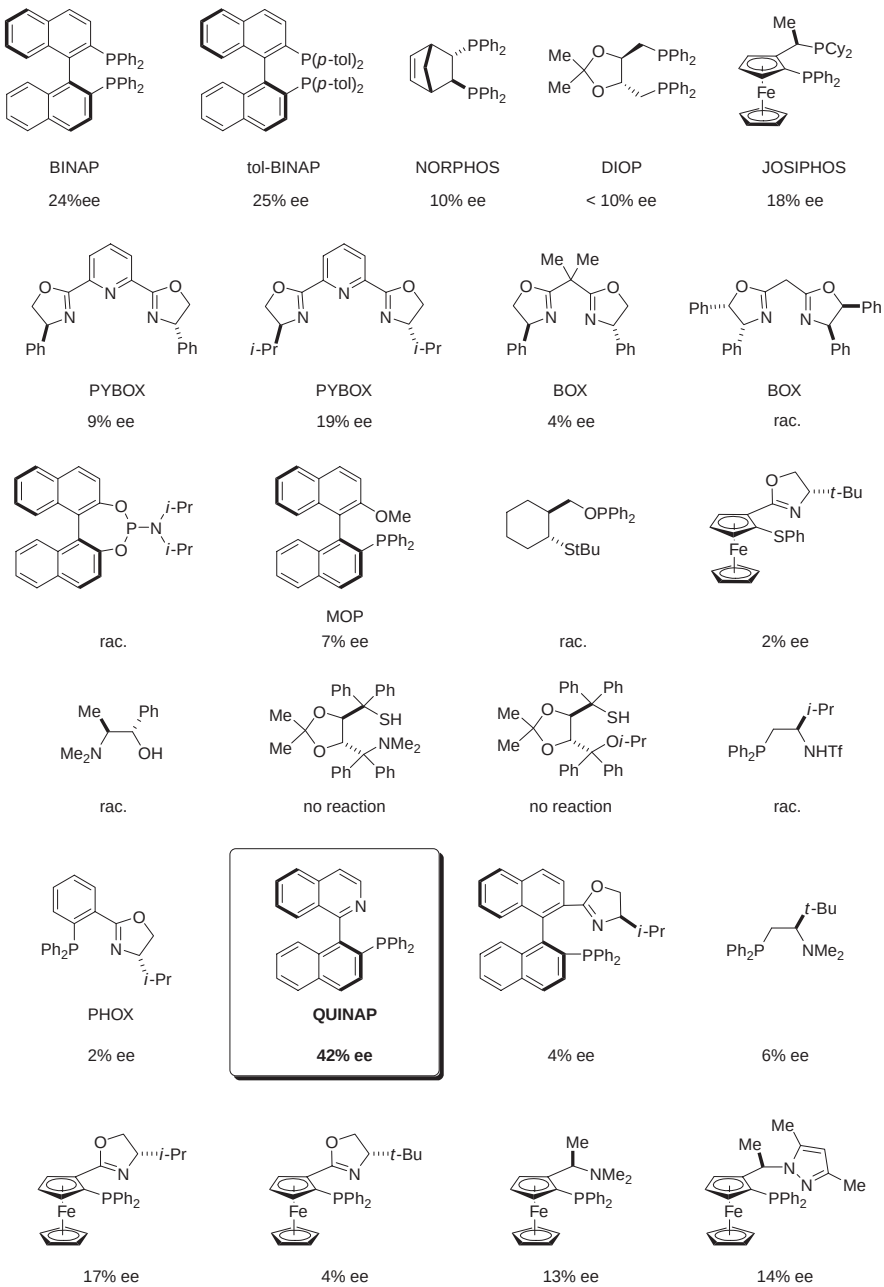


Fig. 11. Ligand screening in the conjugated addition of phenylacetylene to **23** to give **27**. The enantiomeric excess is determined by chiral HPLC analysis after conversion of **27** into anilide **50**.

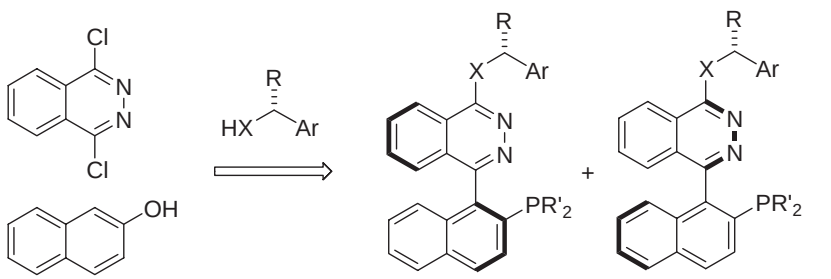
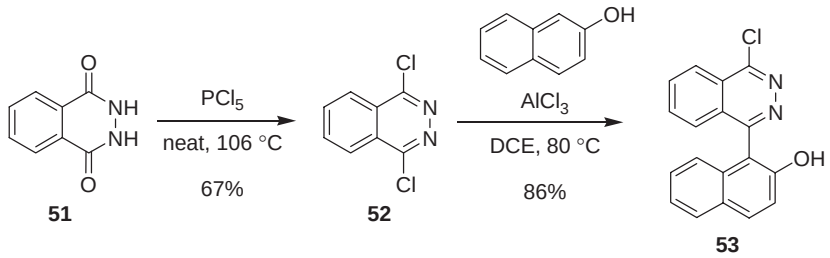
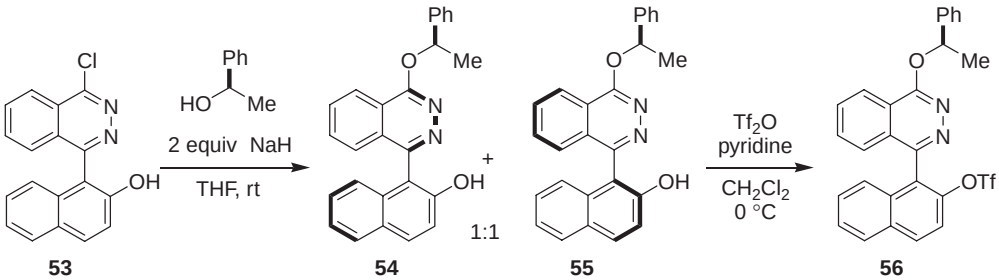


Fig. 12.



Scheme 19.



Scheme 20.

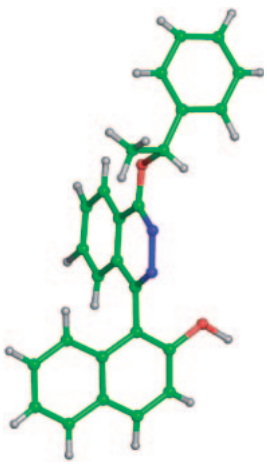
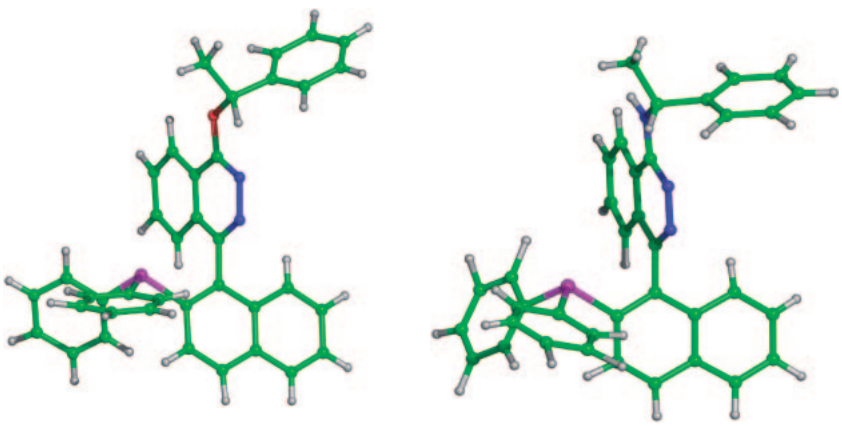


Fig. 13. X-ray structure of **54**.

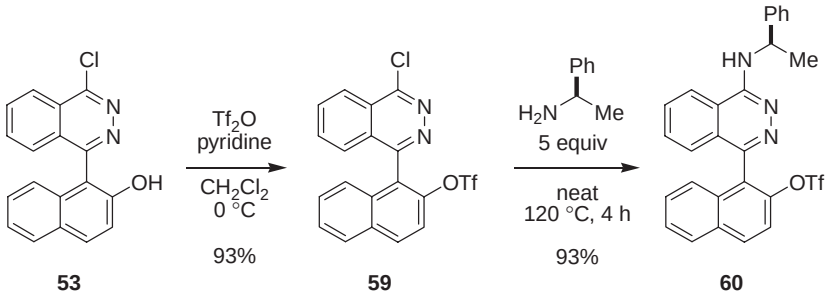
For the synthesis of an analogous structure incorporating a chiral amine, naphthol **53** was first converted into the corresponding triflate **59** in 93% yield by treatment with triflic anhydride and pyridine in CH_2Cl_2 at 0 °C (Scheme 21). Subsequently, (*R*)-α-phenethylamine was coupled at 120 °C under solvent free conditions to give **60** as a 1:1 mixture of diastereomers in 93% combined yield.

Finally, the ligands **61** and **62** are obtained after nickel-catalyzed phosphination in DMF at 120 °C as a 1:1.2 mixture in 80% combined yield. We refer to **61** and **62** as *N*-PINAP. Interestingly, when the reaction is conducted at 100 °C, the (*R*,*P*) isomer **61** is formed preferentially (dr 2.4:1), starting from a 1:1 mixture of **60**. The ligands **61** and **62** are conveniently separated by crystallization or chromatography on silica gel; X-ray crystallographic analysis of **61** established the configuration unambiguously (Fig. 14).



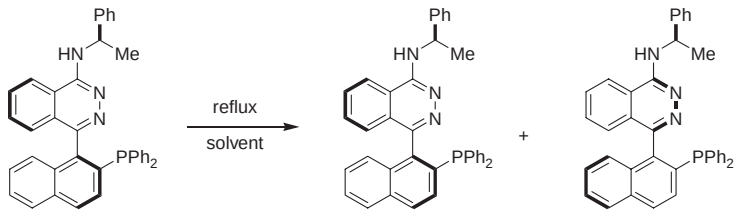
57 **61**

Fig. 14. Crystal structures of **57** and **61**.

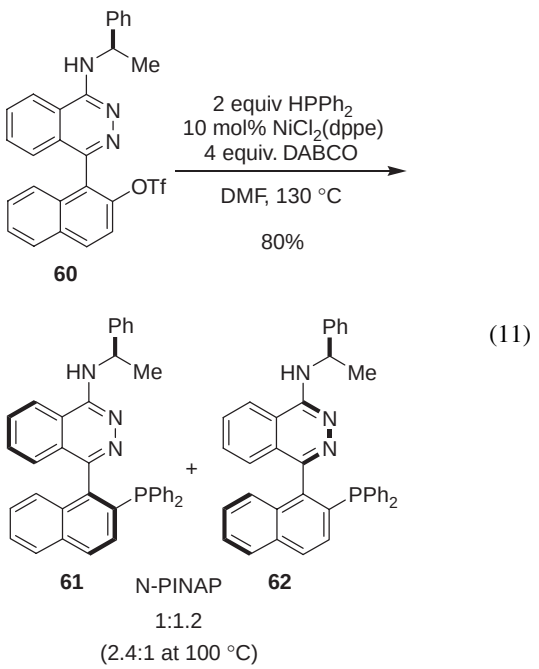


Scheme 21.

Table 1. Epimerization of **61** at Different Temperatures



Time/h	*p*-Xylene, bp: 138 °C	Toluene, bp: 111 °C	Benzene, bp: 80 °C
4	1:1	3:1	>98:2
8	—	2:1	>98:2
20	—	1:1	>98:2



(11)

3.3.2 Configurational Stability of PINAP Ligands: Because it is known that biaryl structures analogous to QUINAP are sensitive to structural modifications with respect to rotation around the biaryl bond, it was decided to investigate the possible epimerization of the PINAP ligand under various conditions. As a result of the ligand design the two atropisomers are diastereomeric, which allowed straightforward analysis of epimerization. During our initial survey, diastereomerically pure *N*-PINAP **61** was heated to reflux in benzene (bp: 80 °C), toluene (bp: 111 °C) and *p*-xylene (bp: 138 °C), and the formation of the atropdiastereomer **62** was monitored by ^{1}H NMR spectroscopy. After 4, 8, and 20 h samples were taken, and the ratio of the diastereomers was determined by integration of the signals of the methyl protons of **61** and **62** (Table 1).[92] In refluxing benzene at 88 °C no epimerization was observed even after 20 h. In toluene at 111 °C, **62** could be observed in the ^{1}H NMR, and after 20 h the two diastereomers **61** and **62** were present in a 1:1 ratio. In *p*-xylene at 138 °C the diastereomers seem to interconvert rapidly, and within only 4 h the 1:1 mixture was observed.

In order to evaluate the energies for the rotation barrier of the PINAP ligands, a kinetic data for the epimerization was obtained. Although the ratio of the two diastereomers could be measured with NMR spectroscopy,[92] the more accurate data were collected using chiral HPLC. In the experimental setup, pure **57** was added to *p*-xylene at different temperatures, aliquots were taken after fixed time intervals, and the samples were analyzed by HPLC (examples are given in Fig. 15).

This set of data allowed us to determine the rate constant for the rotation of biaryl moiety at a given temperature, by plotting $\ln(de_0/de)$ against the time according to the rate law (Fig. 16).[93] The data were collected at four temperatures 100, 110, 120, and 130 °C (Table 2).

An Arrhenius plot of $\ln k_{epi}$ vs. $1/T$ provided the energy of activation E_a for rotation about the biaryl bond in **57**, which is 27.6 kcal mol^{-1} in toluene (Fig. 17). Compared to related biaryl compounds that are commonly used as ligands, the rotational barrier of **57** is rather low (Fig. 18). The rotation barrier of **57** lies in between 1,1′-binaphthyl (24.1 kcal mol^{-1})[94] and

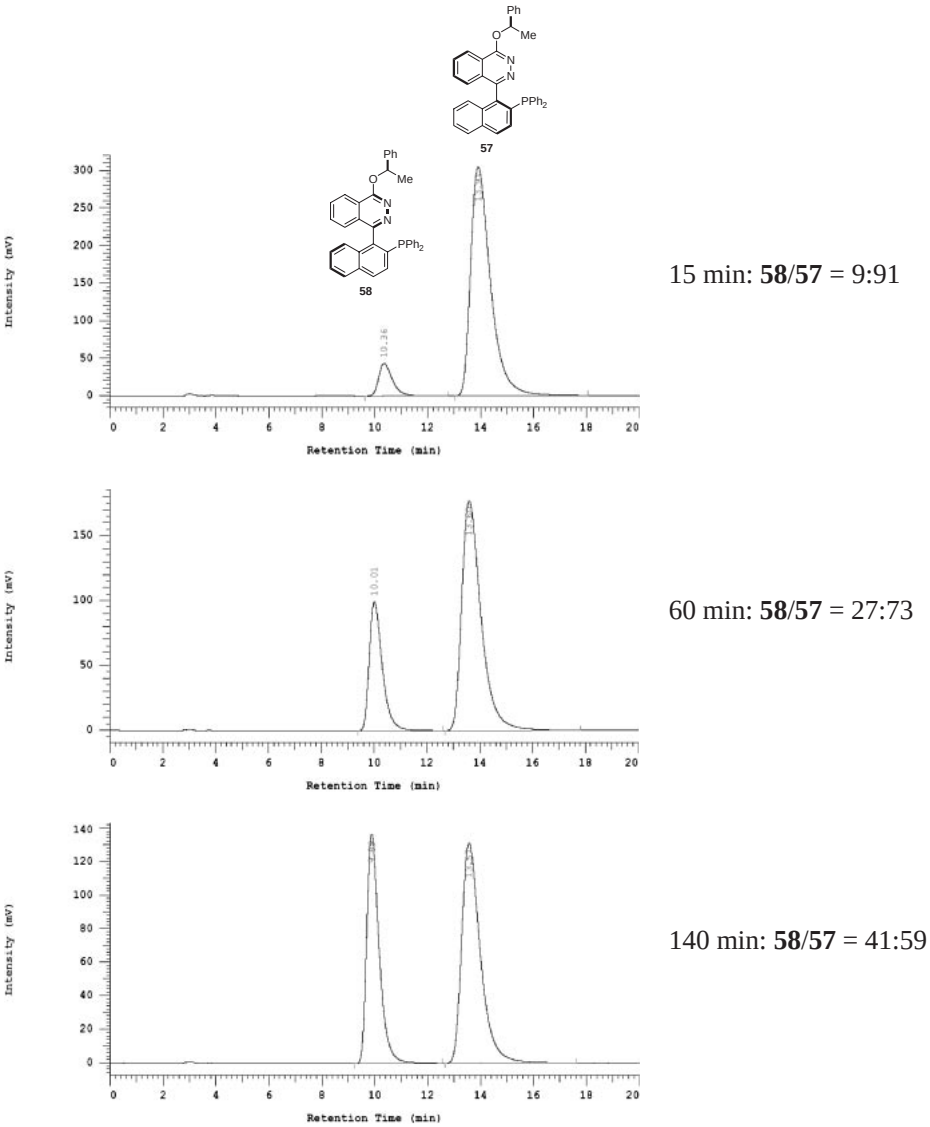


Fig. 15. HPLC traces after different time intervals of the epimerization of **57** in *p*-xylene at 130 °C. Conditions: Chiralcel OD-H; hexane:*i*-PrOH 95:5; 1 mL min^{-1}; detector: UV-absorbance at 254 nm.

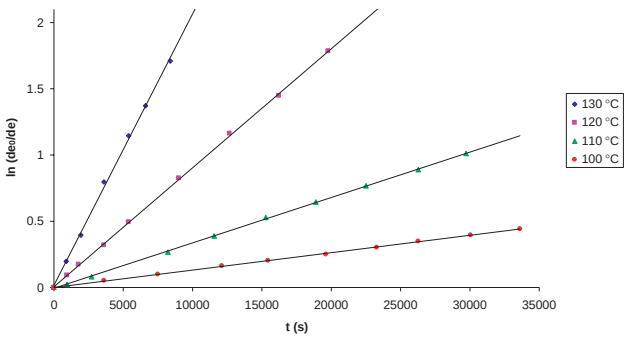


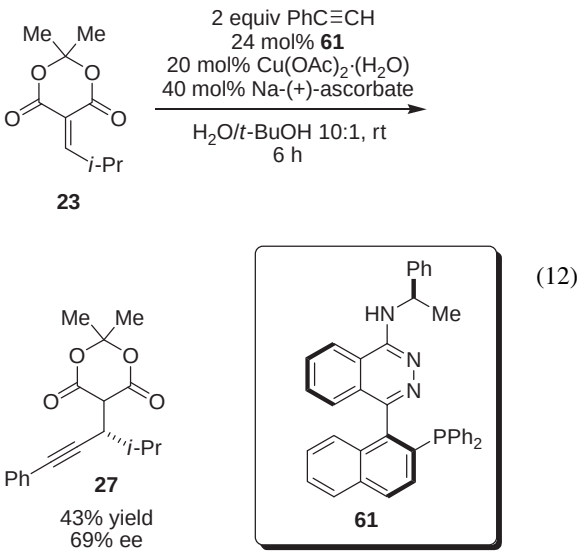
Fig. 16. Determination of the rate constants of epimerization of **57** at different temperatures. Plot of ln(de_0/de) against the time.

IAN-amine (29.8 kcal mol^{-1}).[95] However, the calculated half life $t_{1/2}$ of **57** at 65 °C is more than 25 days, and it is sufficiently stable for a long term storage.

3.4 Enantioselective Conjugate Addition to Meldrum's Acid Derived Acceptors Using PINAP Ligands. With various PINAP ligands in hand, their use in the newly developed copper-catalyzed conjugate addition of alkynes to Meldrum's acid derived acceptors was evaluated. We were pleased to find that *N*-PINAP gave superior results than QUINAP. Using **61** under the same conditions as the initial ligand screening, the addition of phenylacetylene to **23** furnished the product in 43% yield and 69% enantiomeric excess.[96] *O*-PINAP ligand **58** provided similar selectivity to QUINAP (42% ee, Fig. 11), affording the product **27** in 44% ee under identical conditions.

Table 2. Rate Constant of Epimerization of **57** at Different Temperatures in *p*-Xylene

Temperature/°C	k_{epi}/s^{-1}	$t_{1/2}$/h
100	$1.30 \cdot 10^{-5}$	15
110	$3.44 \cdot 10^{-5}$	6
120	$8.99 \cdot 10^{-5}$	2
130	$20.5 \cdot 10^{-5}$	1



(12)

Encouraged by this improvement in enantioselectivity, we moved forward to optimize the reaction conditions. First, the effect of the reaction temperature on the asymmetric induction in the addition of phenylacetylene to **23** using *N*-PINAP **61** was investigated. Lowering from 23 °C (room temperature) to 0 °C (ice-bath) resulted in an improvement of the enantiomeric excess of the product **27** from 69 to 80%. However, the yield of **27** varied between the runs presumably due to the inefficient mixing of the reaction resulting from increasing viscousity of the reaction mixture. This problem could be alleviated by increasing the amount of phenylacetylene from 2 equiv to 10 equiv. Also, the solvent was changed from *t*-BuOH/water mixture to water to ensure better stirring.

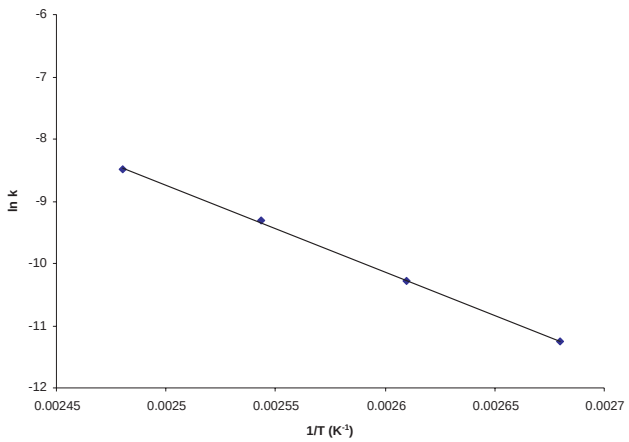


Fig. 17. Determination of the energy of activation E_a for the epimerization of **57**. Arrhenius plot of the rate constants against the temperature.

Under these optimized conditions, we investigated the influence of the ratio of metal to ligand (Table 3). Using a constant amount of 20 mol % of $Cu(OAc)_2 \cdot H_2O$ and 40 mol % sodium (+)-ascorbate, the addition of phenylacetylene (10 equiv) to Meldrum's acid derived acceptor **23** in H_2O at 0 °C was studied with different loadings of *N*-PINAP **61**. Interestingly, the enantioselectively decreased only marginally with a small excess copper present, indicating that this process is likely ligand accelerated. With excess ligand the reaction rate was decreased; a 2:1 ligand to copper ratio lead to complete inhibition of the reaction. We found it optimal to use a 1:1 ligand to copper ratio leading to an improved reaction rate without loss in enantioselectivity.

3.4.1 Mass Spectrum of 61·Cu^{I}: In order to get further information on the complex formed between Cu^{I} and PINAP, isolation and characterization of the copper–*N*-PINAP complex was attempted. After reduction of $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in water with sodium (+)-ascorbate (2 equiv), **61** (1 equiv) was added followed by phenylacetylene (50 equiv). The resulting mixture was stirred for 10 min, then the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was a yellow powder, which could not be analyzed by NMR spectroscopy due to signal broadening that is likely to be caused by the presence of paramagnetic Cu^{II}. The powder was subjected to mass spectroscopic analysis. In the high-resolution MALDI-TOF mass spectrum, the major peak corresponded to **61**·Cu^{+} with an observed exact mass of 622.1457 Da (calculated: 622.1468). The peak with the highest mass corresponded to the dimeric complex (**61**)$_2$·Cu^{+}, also dectected in small amounts was the peak for **61**·Cu^{2+} (Fig. 19). This is consistent with the presence of a copper(I)–*N*-PINAP 1:1 complex as the major species.

3.4.2 Optimization of the Ligand Structure: As it was found that the chiral amine moiety of the PINAP has significant effect on the enantioselectivity, it was decided to prepare PINAP ligands analogous to **61**. Initial studies showed that modifications on the aromatic group of the amine exerted little

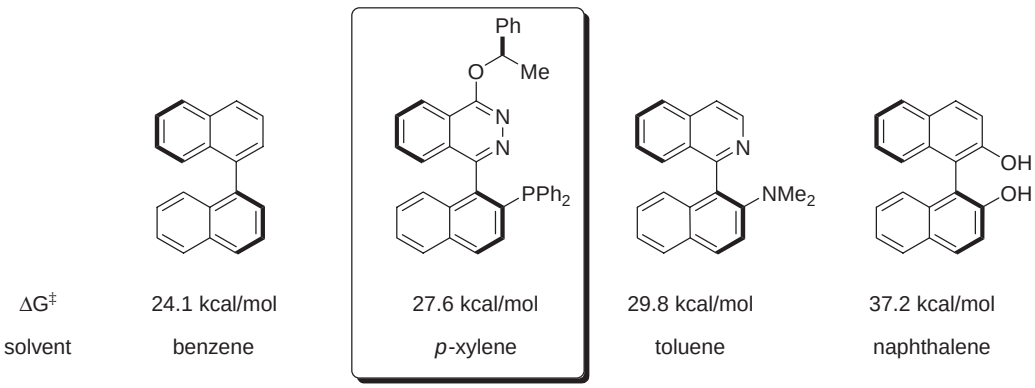
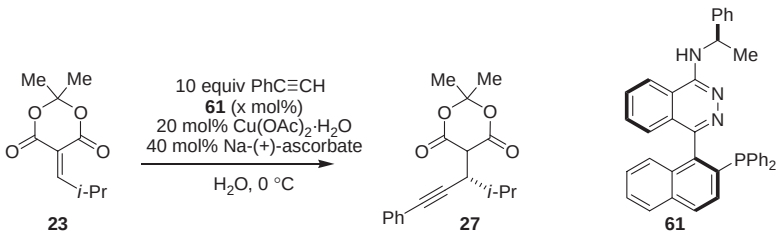


Fig. 18. Rotation barriers of **57** and related biaryl compounds.

Table 3. Effect of the Copper to Ligand Ratio on the Enantioselectivity and Conversion in the Addition of Phenylacetylene to **23**



Ligand loading/mol %	Ratio **61**:Cu	ee[a]/%	Conversion[b]/%	Time/h
5	0.25:1	42	40	18
10	0.5:1	68	84	20
15	0.75:1	69	74	18
20	**1:1**	**79**	**76**	**20**
24	1.2:1	80	58	18
40	2:1	n.d.	<5	14

a) The enantiomeric excess was determined after conversion into the corresponding anilide **50** (Scheme 18). b) The conversion was determined by analyzing the ratio **23** and **27** in the ^{1}H NMR after filtration of the reaction mixture through a plug of silica gel and concentration.

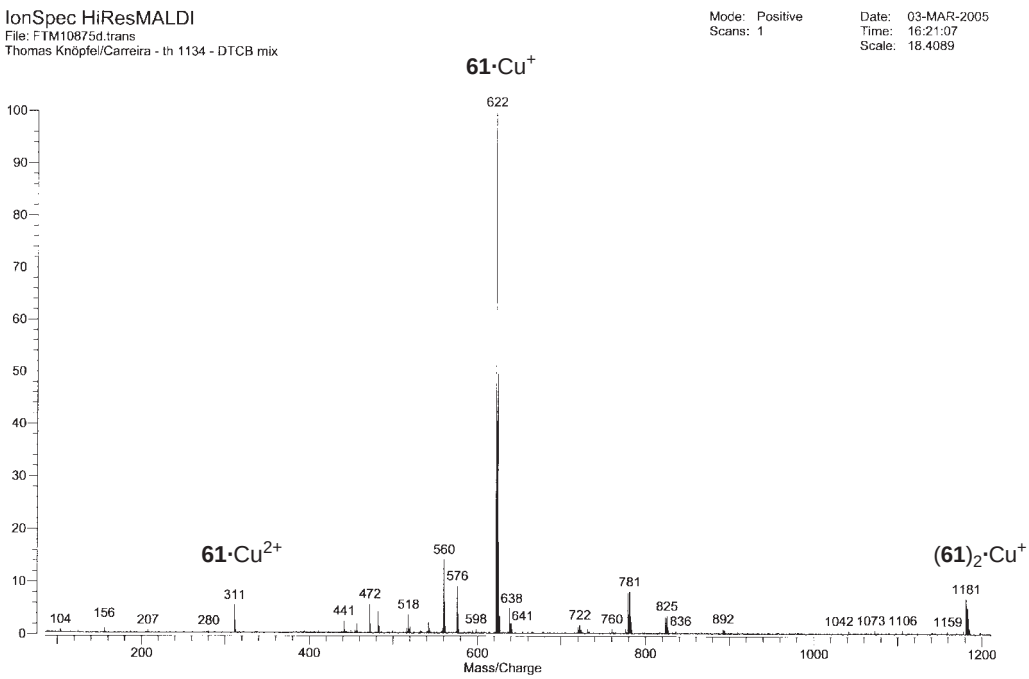
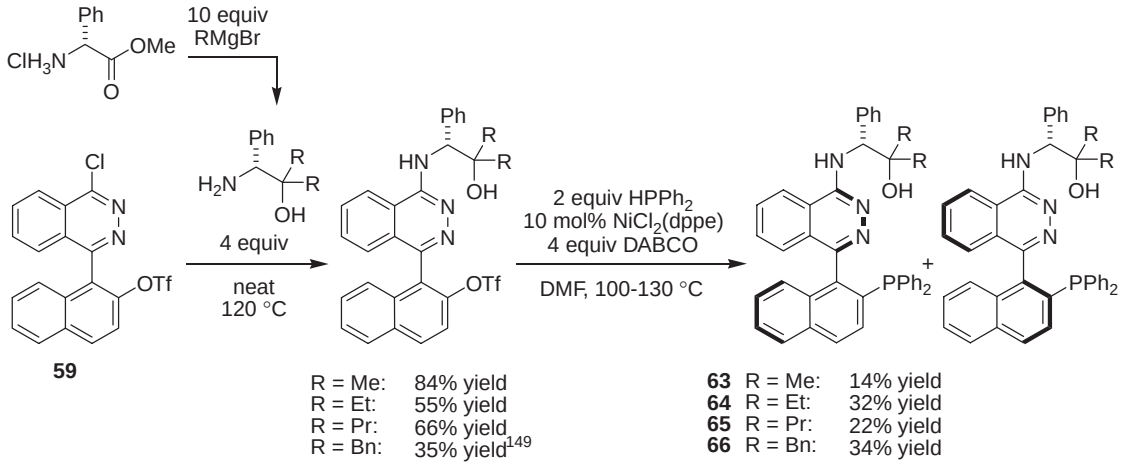


Fig. 19. MALDI-TOF mass spectrum of in situ prepared Cu^{I}·**61**.

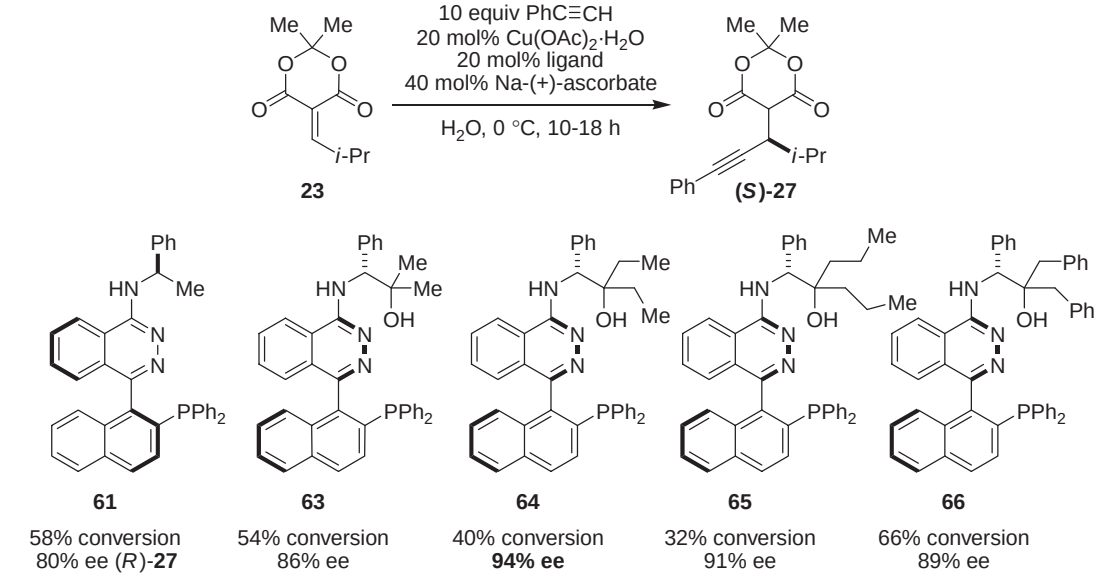
influence on the enantioselectivity. Subsequently, the aliphatic residue was modified. A variety of chiral amines can be easily accessed from inexpensive phenylglycinemethyl ester hydrochloride by double addition of Grignard reagents.[97] A series of different amines (R = Me, Et, Pr, Bn, and Ph) were coupled to the chlorophthalazine core of triflate **59** at 120 °C to give the products in 35–84% yield (Scheme 22).[98] The addition of the sterically very demanding (*R*)-2-amino-1,1,2-triphenylethanol (R = Ph) failed to afford the desired adduct and resulted in recovery of starting materials. After nickel-catalyzed phosphination the diastereomers were separated, and the *R,M* atropisomers **63–66** were isolated in 14–34% yield. Subsequently, these PINAP were tested in the conjugate addition of phenylacetylene to **23**.

It was exciting to find that ligands **63–66** furnished the adduct **27** with synthetically useful enantioselectivities (Scheme 23). The dimethyl derivative **63** provided the adduct **27** in 86% ee, the diethyl derivative **64** proved to be optimal, providing the adduct in 94% ee. Ligands bearing substituents larger than ethyl led to slightly decreased enantioselectivities. The dipropyl ligand **65** furnished **27** in 91% ee and the dibenzyl ligand **66** gave rise to the adduct in 89% ee.

After having found a way to increase the enantioselectivity, we then turned our focus on the improvement of the reaction



Scheme 22.

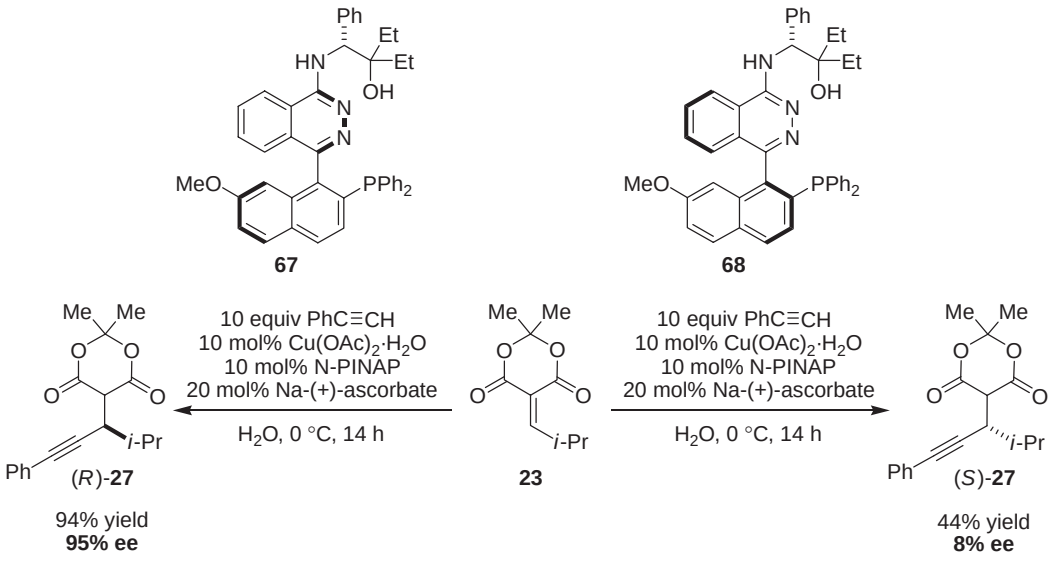


Scheme 23.

rate. Various modifications of the naphthyl portion of the PINAP were undertaken. During the course of this investigation, it was discovered that the incorporation of the methoxy group at the 7-position of *N*-PINAP led to a vast improvement in the reaction rate of the copper-catalyzed conjugate addition of phenylacetylene. This finding compelled us to synthesize a hybrid ligand, which incorporated both improvements on PINAP, i.e. the novel aminoalcohol and the 7-methoxy group, that would hopefully allow the combination of both high enantioselectivity and reaction rate. Gratifyingly, 7-methoxy ligand **67**[80b] furnished the product in 95% ee and full conversion of the reaction was achieved within a reasonable time scale. Owing to the higher activity of the catalyst, the loading could even be lowered to 10 mol % without effecting the enantioselectivity; the adduct **27** was formed in 94% yield and 95% enantiomeric excess at 0 °C in 14 h (Scheme 24). Strikingly, atropisomeric ligand **68** gave rise to almost complete loss of asymmetric induction, providing the product in only 8% enantiomeric excess.

With highly active and selective catalyst in hand, the scope of the reaction was examined (Fig. 20). With only 10 mol % of **67**, high yields and enantioselectivities were observed for the acceptors with γ-branched substituents. For substrates without γ-branching, 20 mol % catalyst loading was necessary to achieve full conversion and slightly lower enantioselectivities were observed (R = Et and *i*-Bu, Fig. 20). The reactions with acceptors derived from aromatic aldehydes are relatively sluggish, and the prolonged reaction times were required for the reaction completion (R = Ph and *m*-tolyl). The enantioselectivities of the products can be further enhanced by simple recrystallization. For example, the enantiomeric excess of **72** was improved from 90% ee (87% yield) to 98% ee (60% yield) by crystallization from ethyl acetate.

Aliphatic alkynes also participated in the conjugate addition to Meldrum's acid derived acceptors using **67**, however, the yield of the product was significantly lower and also the enantioselectivity was decreased. For example, the conjugate addition of 4-phenyl-1-butyne to **23** gave only 29% yield of **24** with 68% ee, even after 24 h at 20 °C using 20 mol % of **67** (Eq. 13).



Scheme 24.

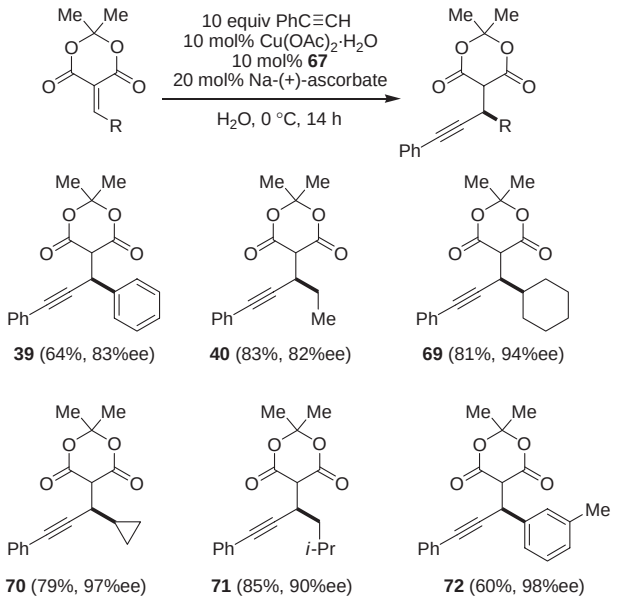
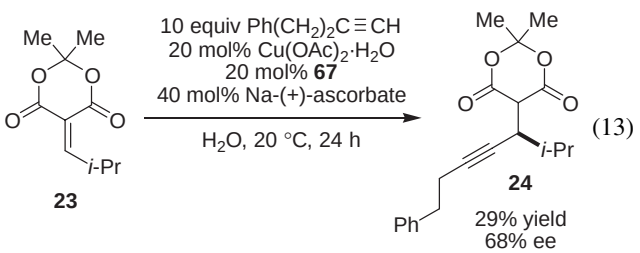
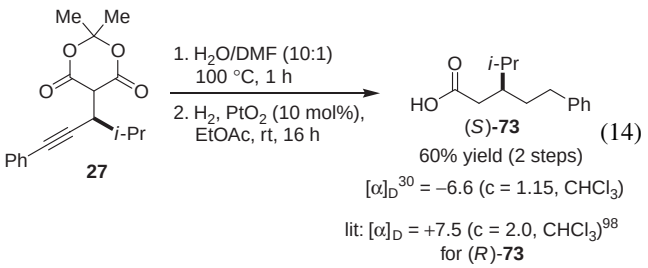


Fig. 20. Enantioselective conjugate addition of phenylacetylene to Meldrum's acid derived acceptors.



(13)

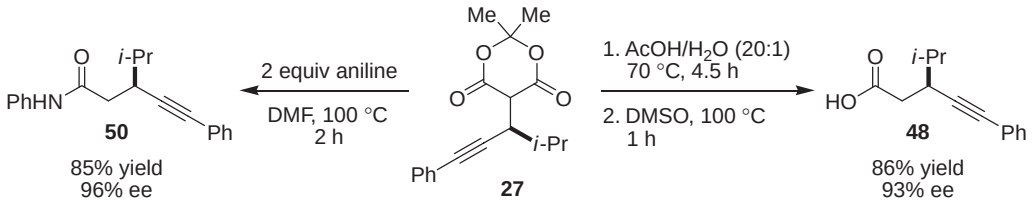
The excess amount of alkyne was necessary to ensure efficient stirring of the reactions mixture when the reactions are run at small (0.25 mmol) scale. However, additional experiments showed that the amount of alkyne could be reduced to 1 equiv without compromising the selectivity when the reaction is run on a larger scale (1.25 mmol).[80b] The absolute configuration of **27** was determined by correlating to a known compound. The adduct **27** was converted into the corresponding carboxylic acid by heating in DMF/H_2O 10:1 at 100 °C for 1 h (Eq. 14), subsequently the alkyne was reduced with Adams' catalyst (PtO_2) in EtOAc to furnish 4-methyl-3-phenethylpentanoic acid (**73**) in 60% over two steps (unoptimized conditions). Comparison of the optical rotation with a value reported in the literature proved the absolute configuration at C_β to be *S*.[99]



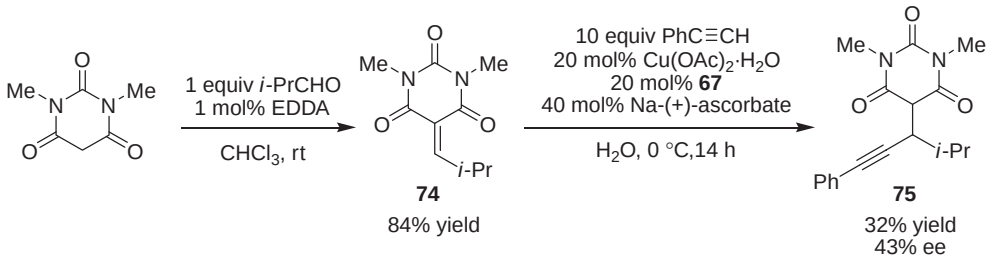
(14)

In order to demonstrate that the products from the conjugate addition can be converted into useful building blocks. For example, **27** was converted to both the corresponding anilide **50** and the carboxylic acid **48** (Scheme 25). Under optimized condition the adduct **27** was converted into **50** by heating it in the presence of 2 equivalents of aniline for 2 h in DMF to 100 °C. The product was obtained in 85% yield and 96% enantiomeric excess. The conversion into the corresponding carboxylic acid was best carried out in a two step sequence. Hydrolysis of the acetal in AcOH/H_2O 20:1 at 70 °C furnished the dicarboxylic acid, which was decarboxylated in DMSO at 100 °C to provide **48** in 86% yield (two steps) and 93% enantiomeric excess.[100] The alternative one step protocol using DMF/H_2O 10:1 at 100 °C gave rise to **48** in consistently good yields, but the enantiomeric excess of **48** ranged form 85–94% ee.

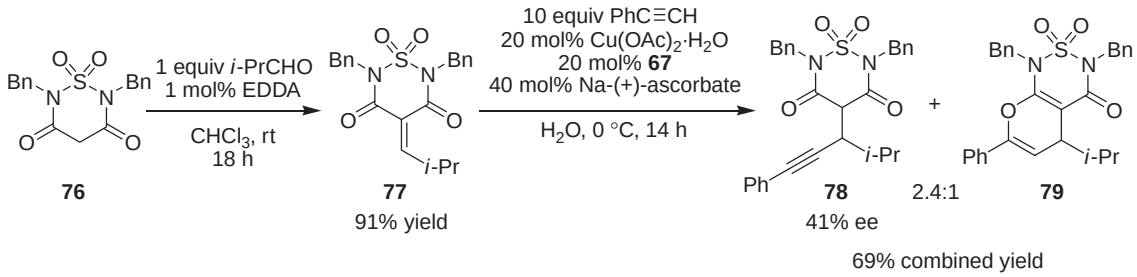
3.4.3 Conjugate Addition to Related Acceptors Using 67: Using the conditions established above, the conjugate addition to other types of acceptors was also investigated. Acceptor **74**, prepared form *N*,*N*′-dimethylbarbituric acid and isobutyralde-



Scheme 25.



Scheme 26.



Scheme 27.

hyde, was a suitable substrate. Under the standard condition, the adduct **75** was furnished in 32% yield and 43% enantiomeric excess using 20 mol % PINAP **67** at 0 °C for 14 h (Scheme 26).

An analogous acceptor **77** bearing a sulfonyl functionality was also used as a substrate. It was prepared by condensation if isobutyraldedhyde with **76** under standard conditions in 91% yield (Scheme 27). Interstingly, addition of phenylacetylene to **77** furnished expected product **78**, that is formed in 41% enantioselectivity, and the postulated byproduct **79**[101] a 2.4:1 ratio. The byproduct **79** results from addition of a carbonyl oxygen into the alkyne which is likely facilitated by π-coordination of Cu^{I} to the alkyne.

4. Conclusion

As the application of in situ generated metal alkynylides, two novel conjugate addition processes were developed. First, in situ generated zinc alkynylides using $Zn(OTf)_2$, triethylamine and a terminal alkyne was successfully applied in diastereoselective conjugate addition to the chiral oxazepane acceptors. The adducts obtained could be converted into highly enantiomerically enriched β-alkynyl carboxylic acid, a class of compound that is otherwise difficult to access.

Subsequently, a novel protocol for the copper-catalyzed conjugate addition of aromatic alkynes to Meldrum's acid derived acceptor was developed. The reactive copper species is formed in water by reduction of $Cu(OAc)_2 \cdot H_2O$ with sodium (+)-ascorbate. A range of adducts were obtained, which could be conveniently converted into the corresponding β-alkynyl carboxylic acids. This process represents the first example of a conjugate addition of terminal alkynes involving copper-catalysis.

This copper-catalyzed methodology was devised into an asymmetric process by the use of chiral ligands. In a survey of a large number of candidates we identified QUINAP as a ligand leading to modest enantiomeric induction. Because of its limited availability and difficulty in modifying its core structure, we developed a novel class of atropisomeric P,N-ligand PINAP incorporating as a phthalazine a N-donor. This ligand class is easily accessible form inexpensive starting materials in a four-step sequence. The separation of the atropisomers is facilitated by forming diastereomers with the installation of another chiral element, that concominantly provided a handle for structural diversity. We have determined the rotation barrier of PINAP at the biaryl linkage, and the energy barrier of 27.6 kcal mol^{-1} was obtained with kinetic measurements. This corresponds to a calculated half life of more than 25 days at 65 °C.

The PINAP ligands have been applied in the copper-catalyzed conjugate addition of alkynes, developed our group. The use of *N*-PINAP provided synthetically useful asymmetric induction (up to 80% ee). In the optimization of the reaction conditions, an unanticipated strong match/mismatch effect between the atropisomerism and the remote stereogenic center of

the chiral controlling group in PINAP ligands was observed. This prompted us to investigate several modifications of the chiral amine moiety of PINAP with respect to enantioselectivity in the conjugate addition. PINAP ligand **67** bearing a chiral amino alcohol, that is readily available from phenylglycine methyl etster can provide enantioselectivities exceeding 90% ee. In addition, the incorporation of a methoxy group at the 7-position of the naphthalene led to improved reaction rates in the conjugate addition of phenylacetylene to the Meldrum's acid derived acceptors. The optimized PINAP ligand furnished a series of conjugate addition adducts in 64–94% yield and 82–97% ee. This protocol represents one of the very few methods for the catalytic, enantioselective conjugate addition of a terminal alkyne. The direct use of a terminal alkyne without need for a separate metallation step enhances the practicality and synthetic utility of this process. The reaction is carried out under remarkably mild conditions using water as reaction medium without recourse to inert atmosphere.

In summary, we have presented two new methods for the catalytic stereoselective conjugate addition of terminal alkynes. In the context of this study we have developed a new class of atropisomeric P,N ligand, PINAP. These ligands are readily available and were of fundamental importance for the success of the enantioselective conjugate addition. These conjugate addition products are readily transformed into β-alkynyl acids which are versatile building blocks in organic synthesis. The extension of these processes as well as application of PINAP ligands in other asymmetric transformations are currently studied in these laboratories.

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