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Enantioselective Alkynylation of Aldehydes Catalyzed by [2.2]Paracyclophane-Based Ligands

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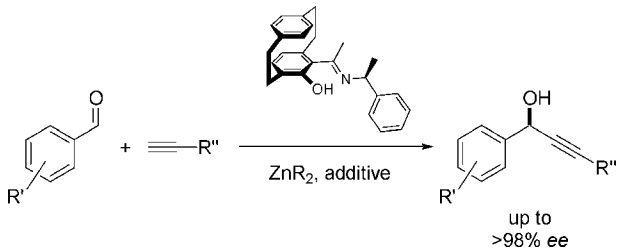
ABSTRACT



[2.2]Paracyclophane-based ketimine ligands were evaluated as catalysts for the enantioselective addition of in situ-prepared alkynylzinc reagents to aldehydes. The initial high activity and enantioselectivity of these ligands could be improved by an additive screening. The final protocol gives chiral propargyl alcohols in up to >98% ee.

Alkynylzinc additions to aldehydes represent an interesting class of reactions of zinc reagent mainly for the following reasons. First, the products, chiral propargylic alcohols, are important precursors to many chiral organic compounds.[1] Second, the process as such can be conducted using several different protocols[2] that apparently all rely on different mechanisms. In their initial report on the addition of alkynylzinc reagents to aldehydes, Ishizaki and Hoshino used a protocol to prepare the active zinc reagent by refluxing a terminal alkyne with diethyl or dimethylzinc in THF. Depending on the stoichiometry, alkyl-alkinylzinc or di-alkynylzinc species are formed.[3] The latter are scarcely soluble in unpolar solvents and usually give a lower selectivity in the addition to aldehydes in the presence of chiral pyridyl alcohol ligands.

A mechanistically different approach by Carreira and co-workers initially used stoichiometric amounts of *N*-methyl-ephedrine and $Zn(OTf)_2$ in the presence of Et_3N to prepare the zinc reagent, which most likely is a alkynylzinc complex of *N*-methylephedrine.[4,5] Excellent results were obtained for aliphatic aldehydes, and the method could even be run solvent-free with catalytic amounts of ligand and metal.[4d]

Recently, Xu and Pu took advantage of the fact that, in the presence of a suitable catalyst or ligand, the deprotonation of a terminal alkyne by diethylzinc occurs even at room temperature in THF.[6] In the presence of bulky BINOL-based ligands, good to excellent enantioselectivities were achieved for aromatic aldehydes.

Despite the achievements made in this field of zinc chemistry, the alkynylation of aldehydes has not yet reached the level of practicability that is required for a synthetically useful *catalytic* reaction. In all examples cited above, high loadings of ligands (10 to >100%) had to be employed to achieve good selectivity. In many cases, the gram amount of the employed ligand exceeded the amount of substrate.

(1) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.
(2) For a recent review, see: Pu, L. *Tetrahedron* **2003**, *59*, 9873.
(3) Ishizaki, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1901.
(4) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *26*, 4233−4236. (c) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. N. *Acc. Chem. Res.* **2000**, *33*, 373. (d) Anand, N. K.; Carreira, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
(5) $Zn(OTf)_2$ is 10 times more expensive than diethylzinc: $Zn(OTf)_2$, 10 g = 46.80 $ (1 euro/mmol); Et_2Zn in hexane, 100 g (810 mmol) = 80.90 euro (0.1 euro/mmol). Prices were taken from Acros Organics.
(6) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555.

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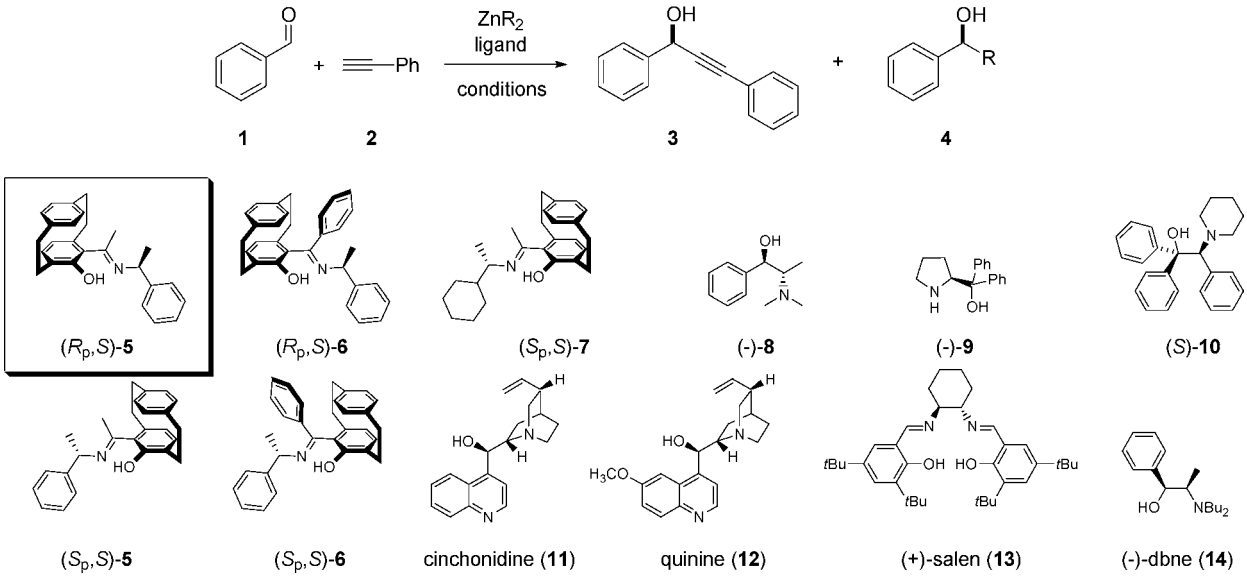
Table 1. Reaction Optimization for the Addition of Phenylacetylene to Benzaldehyde[a]



entry	ligand (mol %)	solvent	additive	temp (°C)	protocol[b]	yield of **3** (**4**) (%)	ee of **3** (%)[c]
1	(R_p,*S*)-**5** (2)	1 mL of hexane		20	A	22 (73)	54 (*R*)
2	(R_p,*S*)-**5** (2)	1 mL of hexane		20	B	36 (60)	58 (*R*)
3	(R_p,*S*)-**5** (2)	1 mL of hexane		20	C	47 (50)	57 (*R*)
4	(R_p,*S*)-**5** (2)	1 mL of hexane, 0.1 mL of THF		20	C	72 (22)	51 (*R*)
5	(R_p,*S*)-**5** (2)	1 mL of hexane, 1 mL of THF		20	C	98	9 (*R*)
6	(R_p,*S*)-**5** (2)	1 mL of hexane, 1 mL of toluene		20	C	63 (33)	40 (*R*)
7	(R_p,*S*)-**5** (2)	1 mL of hexane	MeOPEG (1 mol %)	20	C	76 (20)	64 (*R*)
8	(R_p,*S*)-**5** (2)	1 mL of hexane; 1 mL of toluene	MeOPEG (1 mol %)	20	B	62 (33)	71 (*R*)
9	(R_p,*S*)-**5** (2)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	46 (50)	82 (*R*)
10	(R_p,*S*)-**5** (2)	1 mL of hexane; 1 mL of toluene	MeOPEG (1 mol %)	5	B	50	74 (*R*)
11	(R_p,*S*)-**5** (2)	1 mL of hexane; 1 mL of toluene	MeOPEG (1 mol %)	0	B	72	54 (*R*)
12	(R_p,*S*)-**5** (2)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	D	51	**91** (*R*)
13	(S_p,*S*)-**5** (2)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	44	67 (*S*)
14	(R_p,*S*)-**6** (2)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	66	44 (*R*)
15	(S_p,*S*)-**6** (2)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	48	72 (*S*)
16	(S_p,*S*)-**7** (2)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	51	75 (*S*)
17	(−)-**8** (5)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	66	37 (*S*)
18	(−)-**9** (5)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	79	67 (*R*)
19	(*S*)-**10** (5)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	85	10 (*S*)
20	**11** (10)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	96	7 (*S*)
21	**12** (10)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	95	23 (*S*)
22	(+)-**13** (5)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	74	16 (*S*)
23	(−)-**14** (2)	1 mL of hexane; 2 mL of toluene	MeOPEG (1 mol %)	10	B	86	57 (*R*)
24	(R_p,*S*)-**5** (5)	2 mL of toluene	DiMPEG (2.5 mol %)	10	E	90	**92** (*R*)

[a] All reactions were run on a 0.5 mmol scale. [b] Protocol A: ligand, solvent, additive (as indicated), diethylzinc (1 mL, 1 M in hexane), phenylacetylene (110 μL), 0.5 h, rt, then benzaldehyde (50 μL), 12 h. Protocol B: like protocol A, but all compounds were stirred for 1 h at room temperature before addition of benzaldehyde. Protocol C: like protocol A, but all compounds were stirred for 3 h at room temperature before addition of benzaldehyde. Protocol D: slow addition (5 h) of a mixture of phenylacetylene (110 μL) and diethylzinc (1 mL, 1 M in hexane) to a mixture of ligand, additive, benzaldehyde. Protocol E: like protocol A, but dimethylzinc (0.5 mL, 2 M in toluene) was used instead of diethylzinc. [c] Absolute configurations were assigned by comparison of HPLC traces and optical rotation values with known compounds and the assumption of a unanimous reaction pathway for all substrates.

This is most certainly due to the higher reactivity of the alkynylzinc bond as compared to alkylzinc bonds, which also manifests in the high selectivity for alkynyl vs alkyl transfer when excess diethylzinc is used in the above-mentioned protocols.

Our experience with active zinc species[7] and highly active substrates[8] as well as recent observations of additive effects in organozinc reactions[9] inspired us to take a closer look at the alkynylzinc addition to aldehydes.

In an initial screening, conditions for the in situ formation of alkynylzinc by deprotonation of phenylacetylene with diethylzinc were elaborated (Table 1). In all runs listed in

(7) Dahmen, S.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119.

(8) (a) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940. (b) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int Ed.* **2002**, *41*, 3692.

(9) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850.

Table 1, the conversion of starting benzaldehyde was >95% and the amounts of alkynylation and ethylation product were measured by a calibrated HPLC method.

Stirring both starting materials in the presence of 2 mol % ligand (R_p,*S*)-**5** for 1 h at room temperature and then adding the aldehyde resulted in the formation of **3** in 22% yield and 54% ee (entry 1). If the stirring time before the addition of aldehyde is prolonged to 2 or 3 h, 36 and 47% yield of **3** are obtained (entries 2 and 3). Hence, the deprotonation of phenylacetylene by diethylzinc in hexane is a relatively slow step. This deprotonation, however, is supported by basic additives. In the presence of 10 vol % THF, 72% yield of **3** is obtained (entry 4). However, the ee begins to drop. In a solvent mixture of hexane and THF (1/1), 98% yield of **3** is formed in a disappointing 9% ee (entry 5).

Addition of 1 mol % MeOPEG (poly(ethylene glycol) monomethyl ether, MW 2000) in a solvent mixture of hexane (1 mL of a 1 M diethylzinc solution in hexane) and toluene (1 to 2 mL) improved the enantioselectivity from 58 to 71% ee at room temperature. Lowering the temperature to 10 °C boosted the ee up to 82%. However, at 5 and 0 °C, the enantioselectivity again dropped to 74 and 54% ee, respectively (entries 10 and 11).

Under these conditions, a ligand screening was performed employing a variety of commercially available *N*,*O*-ligands, as well as a set of [2.2]paracyclophane-based ketimines.[10]

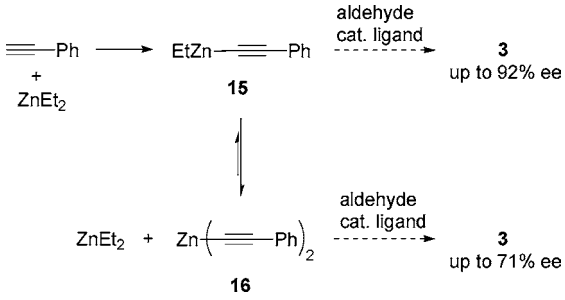
As can be seen from Table 1, most simple amino alcohol ligands do not represent promising catalysts for this reaction (under the chosen conditions). An interesting observation is that secondary amine **9** gives a reasonable 67% ee at 5 mol % ligand loading. Secondary amines usually do not give good results in the diethylzinc addition to aldehydes.

Among the [2.2]paracyclophane-based ligands, initially chosen (R_p,*S*)-**5** gave the best results. Using either a slow addition technique (entry 12) or increasing the catalyst loading to 5 mol % (entry 24, see below) gave rise to the reaction product in >90% ee.

Having found the most effective ligand for the test reaction, we again had to address the problem of selectivity of alkynyl vs alkyl transfer. As the paracyclophane-based ligands depicted in Table 1 are also highly potent ligands for the dialkylzinc addition to aldehydes, the ethylation product **4** is also obtained when larger amounts of diethylzinc are present in the reaction mixture. As already mentioned above, the deprotonation of phenylacetylene in unpolar solvents is rather slow at room temperature in the absence of basic additives. Basic additives and especially THF, on the other hand, drastically diminished the ee. One way out this problem would be the preformation of the desired active zinc species **15** (Scheme 1) by (a) a longer deprotonation time or (b) a deprotonation at higher temperature before the addition of the aldehyde.

However, if an equimolar mixture of diethylzinc and phenylacetylene was stored over a prolonged period of time (2−3 days), a white precipitate formed that could not be redissolved by heating, addition of toluene, or ultrasound. Presumably, the primarily formed mixed ethyl-alkynyl-zinc species **15** disproportionates to give the (insoluble) dialkynylzinc **16** and diethylzinc. This behavior was only observed in unpolar solvents such as hexane and toluene. In THF, the mixed species was apparently stable.[11]

Scheme 1. Equilibrium of Zinc Species



This assumption is supported by the finding that a suspension of the precipitated dialkynylzinc gives the desired product **3** in high yield (90%) but lower ee (72% *ee*).[12] The same effect is observed when the dialkynylzinc is prepared selectively by the reaction of diethylzinc and excess phenylacetylene (2.2 equiv) at elevated temperature (94% yield, 63% ee).

Several attempts were made to improve the enantioselectivity on the basis of the protocol proceeding via dialkynylzinc species **16** (temperature, additives, ligands; results not listed). As these attempts were unsuccessful, we chose to go back to the initial protocol C and substitute diethylzinc for the less reactive dimethylzinc. Gratifyingly, this change in the zinc precursor not only led to drastically better alkynyl vs alkyl addition selectivity (presumably due to the much slower methyl transfer) but also increased the enantioselectivity of the reaction. Finally, DiMPEG 2000 (poly(ethylene glycol) dimethyl ether, MW 2000) proved to be slightly superior to MeOPEG (entry 1 in Table 2).

With this final protocol in hand, we examined the scope of the reaction using a variety of aromatic aldehyde substrates. In nearly all cases, enantioselectivities >90% could be obtained using only 5 mol % ligand (Table 2, entries 1−7). Only *m*-anisaldehyde gave a lower ee of 80% (entry 6). Astonishingly, in the reaction with diethylzinc instead of dimethylzinc, 90% ee is obtained for this substrate (entry 7).

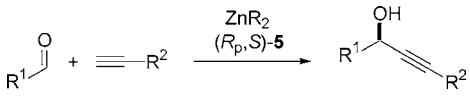
Cyclohexylaldehyde gives lower ee's than the aromatic substrates (entry 9). This supports the literature evidence that for aliphatic substrates, the $Zn(OTf)_2/Et_3N$ protocol seems to be superior.[2] Less acidic acetylenes such as 1-hexyne require a higher deprotonation temperature of 40 °C (entry 10). The addition product is obtained in an unoptimized 84% ee. TMS−acetylene could be employed giving rise to the corresponding addition product in 78% ee (entry 11), while

(10) Dahmen, S.; Bräse, S. *Chem. Commun.* **2002**, 26.

(11) This behavior is atypical for mixed zinc species. The equilibrium could be influenced by the very low solubility of the dialkynylzinc reagents.

(12) Clear supernant solution gives rise to the ethylation product in >80% yield.

Table 2. Scope of Reaction[a]



entry	alkyne	aldehyde (R^1)	yield (%)	ee (%)
1	PhC≡CH	C_6H_5	90	92 (*R*)
2	PhC≡CH	3-Cl−C_6H_4	87	85 (*R*)
3	PhC≡CH	3-Me-C_6H_4	92	90 (*R*)
4	PhC≡CH	4-Cl−C_6H_4	89	95 (*R*)
5	PhC≡CH	2-Br−C_6H_4	86	>98 (*R*)
6	PhC≡CH	3-MeO−C_6H_4	87	80 (*R*)
7[b]	PhC≡CH	3-MeO−C_6H_4	58	90 (*R*)
8	PhC≡CH	1-Napht	86	94 (*R*)
9	PhC≡CH	*c*-C_6H_{11}	82	77 (*R*)
10[c]	1-hexyne	C_6H_5	86	84 (*R*)
11[c]	$(CH_3)_3$SiC≡CH	C_6H_5	83	78 (*R*)
12[c]	$(CH_3)_3$CC≡CH	*c*-C_6H_{11}	52	85 (*R*)
13[b,c]	PhC≡CH	*n*-C_3H_7	85	38 (*R*)
14[c]	1-hexyne	*c*-C_6H_{11}	56	37[d]
15[c]	1-hexyne	C_6H_5CH═CH	86	80 (*R*)

[a] Ligand (R_p,*S*)-**5** (5 mol %), toluene (1.0 mL), DiMPEG 2000 (2.5 mol %), dimethylzinc (0.5 mL, 2 M in toluene), acetylene (1 mmol), 2 h, rt, then aldehyde (0.5 mmol), 12 h, 10 °C. [b] Diethylzinc was used instead of dimethylzinc. [c] Deprotonation was conducted at 40 °C instead of room temperature. [d] Analyzed as the (−)-camphanic acid ester.

the addition of *tert*-butyl acetylene proceeded with 85% ee (entry 12). The addition products of phenyl acetylene to benzaldehyde (entry 13) and 1-hexyne to cyclohexylaldehyde (entry 14) were both obtained with disappointing enantioselectivities (38 and 37% ee, respectively). The 1,2-addition of 1-hexyne to an α,*β*-unsaturated aldehyde proceeded with 80% ee (entry 15).

In retrospect, the described protocols are much more sensitive to slight changes in the reaction conditions than protocols for any other organozinc addition we have encountered so far. From an experimental point of view, the reactivity of alkynylzinc species would be on the same order of magnitude as diphenylzinc (alkylzinc < alkenylzinc < phenylzinc ≤ alkynylzinc).

In summary, different protocols for the enantioselective addition of alkynylzinc reagents to aldehydes were compared. On the basis of the protocol that allows for the lowest catalyst loading, a screening of different commercially available *N*,*O*-ligands as well as several [2.2]paracyclophane-based ketimine ligands was conducted. Due to their high activity, the [2.2]-paracyclophane-based ligands proved to be superior over conventional amino alcohol ligands. The developed protocol reflects the most economic catalyst system so far for the addition of terminal alkynes to aromatic aldehydes in terms of ligand loading and enantioselectivity.

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