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Functionalized carbo- and heterocycles *via* Pt-catalyzed asymmetric alkoxycyclization of 1,6-enynes†

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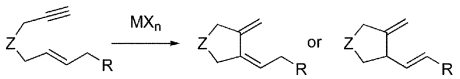
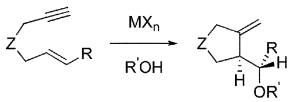
This paper describes the asymmetric version of highly atom-economical alkoxycyclization of 1,6-enynes, using a combination of silver salts with the Pt(II)/(*R*)-Ph-BINEPINE system.

The discovery of new reactions is a major focus of research activity in organic chemistry. Transition metal-catalyzed cyclizations offer ideal conditions in terms of synthetic efficiency and atom economy.[1] Since the seminal and elegant work of Trost, substrates containing two unsaturated functional groups have become excellent partners for such transformations. Among them, 1,6-enynes have shown challenging behaviour and participate in cycloisomerization[2,3] (eqn. 1) and alkoxycyclization[4] (eqn. 2). The latter is of particular interest, because it allows for the simultaneous and stereoselective formation of a C–C and a C–O bond from enynes. The asymmetric version of alkoxy- or hydroxycyclization would provide a valuable synthetic tool for natural or biologically active product syntheses and is to our knowledge still unprecedented. Here we report our preliminary studies on the first Pt(II)-catalyzed asymmetric alkoxycyclization of 1,6-enynes leading to functionalized five-membered carbo- and heterocycles in enantio-enriched form.



(1)

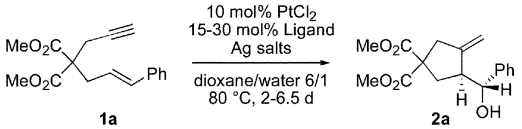


(2)

As the mechanism of this highly atom-economical reaction was found to be similar with both platinum and palladium catalysts,[4a–d] we turned our attention to platinum chemistry and investigated the functionalization of enyne **1a** with platinum in the presence of several chiral phosphane ligands (Table 1). Preliminary tests were performed in dioxane/water 6 : 1 using 10 mol% platinum catalyst and 15 mol% of bidentate or 30 mol% of monodentate phosphane. Even if under these conditions long reaction times are required for the alcohol **2a** to be obtained in high yield, the accelerating effect induced by the phosphorus ligand is quite evident from the fact that only traces of **2a** can be detected when the reaction is run in the absence of any phosphane (entry 1).[5]

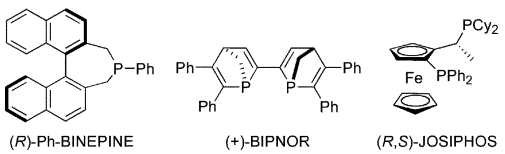
The stereoselectivities obtained in the first batch of experiments were, however, disappointingly low: two digit values were recorded only in three cases with (*R*)-Ph-BINEPINE ((*R*)-phenylbinaphthophosphepine)[6] (entry 3), with (*R*,*S*)-JOSIPHOS (entry 6) and with (+)-BIPNOR, a ligand with stereogenic phosphorus centres (entry 7). The last one was the best chiral inducer of this set, but the *ee* did not exceed 25%. Further improvements were attempted using other chiral ligands, in different co-solvents

Table 1 Ligand and silver salt effect on $PtCl_2$-promoted enyne hydroxycyclization



Entry	Ligand	Ag salts (0.25 eq.)	Time/d	Yield [%]	*ee* [%][a] (config.)
1	/	/	5	0	/
2	(*S*)-NMDPP	/	5	100	5 (+)
3	(*R*)-Ph-BINEPINE	/	6.5	91	20 (+)
4	(*R*)-BINAP	/	5	100	0
5	(−)-DIOP	/	5	72	8 (+)
6	(*R*,*S*)-JOSIPHOS	/	4	91	13 (−)
7	(+)-BIPNOR	/	3	79	25 (−)
8	(*R*,*S*)-JOSIPHOS	$AgPF_6$	4	58	35 (−)
9	(*R*,*S*)-JOSIPHOS	$AgBF_4$	2	65	38 (−)
10	(*R*,*S*)-JOSIPHOS	$AgSbF_6$	2.5	62	41 (−)
11	(+)-BIPNOR	$AgSbF_6$	3	53	33 (−)
12[b]	(*R*)-Ph-BINEPINE	$AgSbF_6$	4	94	85 (+)
13[c]	(*R*)-Ph-BINEPINE	$AgSbF_6$	4	60[d]	85 (+)

[a] The *ee* value was determined by HPLC (Chiralcel OD-H, hexane/propan-2-ol (95 : 5), 1 ml min^{-1}, 215 nm).[8] [b] 5 mol% $PtCl_2$, 60 °C. [c] 5 mol% $PtCl_2$, aqueous acetone, 60 °C. [d] Conversion.



(*R*)-Ph-BINEPINE (+)-BIPNOR (*R*,*S*)-JOSIPHOS

(acetone, toluene, ethylene glycol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, 1,2-dichloroethane…) at various temperature without success.[7]

As it was our feeling that the catalytic performance of our Pt-derivative should have gained from an increased electrophilicity at the metal centre, we undertook to remove the chloride ligands from the coordination sphere of the Pt-phosphane complexes. The activation of Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations and Bayer–Villiger oxidations.[9] To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt/(*R*,*S*)-JOSIPHOS system (entries 8–10), the silver additives had a moderately positive influence on yields and *ee* and the use of $^{-}BF_4$ and $^{-}SbF_6$ salts led consistently to a fair increase of both values. For instance, the hydroxycyclization of enyne **1a** gave the corresponding alcohol **2a** in 62% isolated yield in 2.5 days in up to 41% *ee* (entry 10). A similar trend was observed also with the (+)-BIPNOR-based complex (entry 11). These *ee*'s, however, could not be improved further upon changing co-solvents, temperatures and reagent ratios. In contrast, addition of silver salts to the (*R*)-Ph-BINEPINE-based catalyst had a pronounced positive effect on the rate and allowed the reaction to be run at lower

† Electronic Supplementary Information (ESI) available: General procedure for the asymmetric hydroxycyclization, optical rotation of **2a–d** and **3b–c**. The syntheses of esters derived from **2b** and the determination of absolute configuration are disclosed. See http://www.rsc.org/suppdata/cc/b4/b400908h/

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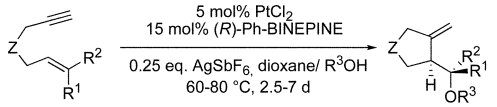
temperature (60 °C) even at halved catalyst loading (5 mol%). These conditions were found to be the best suited for a high yield (94% in four days) to be matched by a substantial enantioselectivity (up to 85%) (entry 12). Once again, various modifications of the reaction conditions did not give better results.[7] For example, when the reaction is conducted in aqueous acetone[4d,e] (entry 13), a similar *ee* is obtained but the conversion does not increase beyond 60%.

The scope of this new asymmetric reaction was then assessed on some enynes in view of its utilization in the asymmetric synthesis of natural compounds of biological interest such as *Podophyllum* lignans or their aza-analogues[10] where the accessibility of the aryltetralin fragment *via* this route has been already demonstrated.[11] While allyl propargyl ethers[4a] were found to be poorly suited substrates for this reaction and led to unpractical mixtures of compounds, carbo- and azo-type enynes **1a–d** reacted smoothly under mild conditions giving the cyclic product in high selectivity (Table 2).

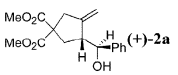
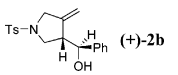
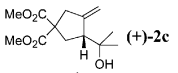
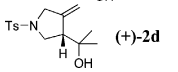
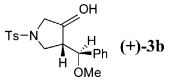
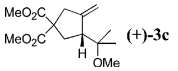
The malonate-derived enyne **1a**, the *N*-tosylated substrate **1b** and the *gem*-dimethyl substituted enynes **1c** and **1d** all performed well in the hydroxycyclization with Ph-BINEPINE. The chemical yields ranged from good to excellent while the *ee*'s were between 56% and 85% (entries 1–4). The asymmetric reaction did work also when methanol was used as the solvent and this allowed us to introduce a methoxy group in the place of the hydroxyl. Thus, from the substrate **1b** and **1c**, the relevant methyl ethers were obtained in 78% and 50% *ee* respectively (entries 5 and 6). The absolute configurations of the alcohols obtained from hydroxycyclizations were determined by empirical methods from the ^{1}H NMR spectra of the *O*-methylmandelate esters **4** derived from **2b** (see ESI†).[12]

In conclusion, we have developed the first enantioselective Pt-promoted enyne alkoxycyclization in up to 85% stereoselectivity.

Table 2 $PtCl_2$-promoted enyne alkoxycyclization



1a, **1b** (Z = $C(CO_2Me)_2$, NTs, R^1 = H, R^2 = Ph)
1c, 1d (Z = $C(CO_2Me)_2$, NTs, R^1 = R^2 = Me)
2a-d (R^3 = H)
3b-c (R^3 = Me)

Entry	Substrate	Time/d	Yield [%]	Product	*ee* [%]
1	**1a**	4	94	 **(+)-2a**	85
2	**1b**	7	86	 **(+)-2b**	84
3	**1c**	3.5	87	 **(+)-2c**	66
4	**1d**	6.5	57	 **(+)-2d**	56
5	**1b**	2.5	49	 **(+)-3b**	78
6	**1c**	5.5	100	 **(+)-3c**	50

[a] The *ee* value was determined by HPLC (Chiralcel OD-H or Chiralpak AS-H). [b] Reaction at 80 °C in screw-capped tube.

This ideal atom-economical reaction leads to the corresponding functionalized five-membered carbo- and heterocycles in good to excellent yields. The use of silver salts combined with (*R*)-Ph-BINEPINE, a monophosphane atropisomeric ligand, is by now the best suited combination for high enantioselectivities to be obtained in this reaction, and the first C–C application with this ligand. Further studies aimed at expanding the synthetic scope of this new asymmetric reaction and at establishing the reaction path and structure of the catalytic species are currently in progress.

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