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Catalytic asymmetric ring-opening of cyclopentadiene–heterodienophile cycloadducts with organometallic reagents*

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Abstract: An unprecedented catalytic asymmetric ring-opening of easily accessible 2,3-heterosubstituted norbornenes with hard alkyl metals (R-M), is able to give a practical regio- and stereoselective access to hetero-functionalized alkyl cyclopentenes in an enantio-enriched form. The copper-catalyzed desymmetrization reaction with trialkylaluminums of sterically hindered and rigid, tri- or tetracyclic Diels–Alder adducts, easily available by cycloaddition reaction of cyclopentadiene with 4-phenyl-urazole and 2,3-phthalazine-1,4-dione, proved to be particularly efficient. Interestingly, the chirality of the amine part of the BINOL-based phosphoramidite is able to impose the absolute stereochemistry of the corresponding adducts.

Keywords: asymmetric catalysis; ring-opening reactions; copper catalysis; organozinc reagents; organoaluminum reagents.

INTRODUCTION

The copper-catalyzed allylic substitution reaction making use of organometallic reagents has generated a great deal of interest in recent years [1]. The advantages of the use of copper are that a broad range of organometallic compounds can be used, and that the regioselectivity is often of the S_N2'-type. We recently reported that small-ring heterocycles, such as epoxides and aziridines, are valuable leaving groups in copper-catalyzed asymmetric allylic alkylations with organometallic reagents [2]. In our continuing interest for the development of new ring-opening reactions of heterocyclic rings to give synthetically useful enantiomerically enriched building blocks, we envisioned 2,3-heterosubstituted norbornenes, such as compounds **1** and **2**, as possible substrates of an allylic alkylation-type reaction (Fig. 1). In fact, looking at the formula, the heteroatoms in positions 2 and 3 of the ring are allylic with respect to the double bond, and the ring is relatively strained; therefore, the C-heteroatom bond could represent an internal point of fracture. These starting materials can easily be prepared by cycloaddition reaction of cyclopentadiene and aza-heterodienophiles, in accordance with previously described procedures [3].

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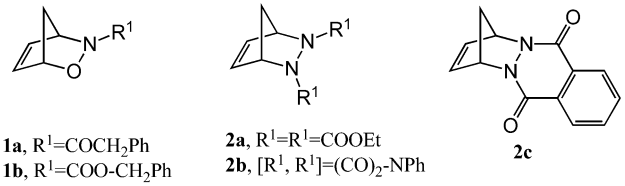
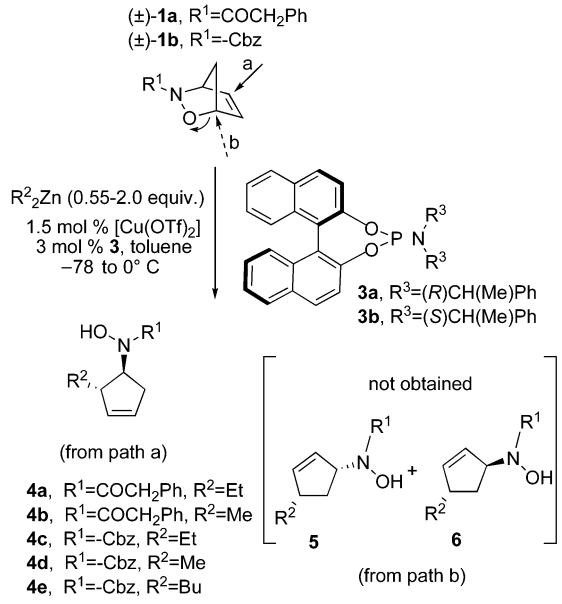


Fig. 1 2,3-Heteronorbornenes **1** and **2** used as starting material for asymmetric C–C bond formations.

We began our study with oxazabicyclic systems, considering that these compounds can be subjected to several transformations, but mainly focused on the cleavage of the N–O bond to give amino alcohols [4]. Other possibilities regard the addition of heteronucleophiles under the catalysis of palladium or by the use of Lewis acids [5]. As for the addition of organometallic reagents, we had noticed a ring-opening of 3-aza-2-oxabicyclo[2.2.1]hept-5-enes of type **1** with Grignard reagents in combination with catalytic amounts of $CuCl_2$. However, the reaction was not completely regio- and stereoselective, and the main product, racemic *anti*-1,2-hydroxamic acids of type **4** (through path a, Scheme 1), were invariably obtained in a mixture of ring-opened products of types **5** and **6**, in which the attack of the organometallic reagent had occurred at the bridgehead carbon atom (path b, Scheme 1) [6]. When we tried to use an alternative approach based on the use of organozinc reagents in the presence of catalytic amounts of copper-complexes with BINOL-derived phosphoramidites of type **3** [7], we found a dramatic increase in the regio- and stereoselectivity, and in practice only hydroxamic acids of type **4** were isolated. The copper catalyst efficiently promotes the addition of the organometallic reagent on the double bond, with cleavage of the C–O bond, accompanied by allylic rearrangement. The corresponding blank reactions performed without the use of phosphoramidite ligands gave a mixture of products and a lower conversion rate.



Scheme 1 Regio- and stereoselective addition of dialkylzinc reagents to racemic 3-aza-2-oxabicyclo[2.2.1]hept-5-enes.

When the reaction was performed with Et_2Zn (0.55 equiv), in accordance with a kinetic resolution protocol, it was possible to obtain **4a** with a 44 % ee at 45 % conversion. A slightly better enantioselectivity (56 % ee at 52 % conversion) was obtained with the use of Me_2Zn. When the kinetic resolution reaction was carried out with diastereoisomeric ligand (*R*,*S*,*S*)-**3b**, a very low enantioselectivity was obtained. Similar results were obtained with compound **1b**, containing an easily removable carbobenzyloxy (Cbz) protecting group on the nitrogen.

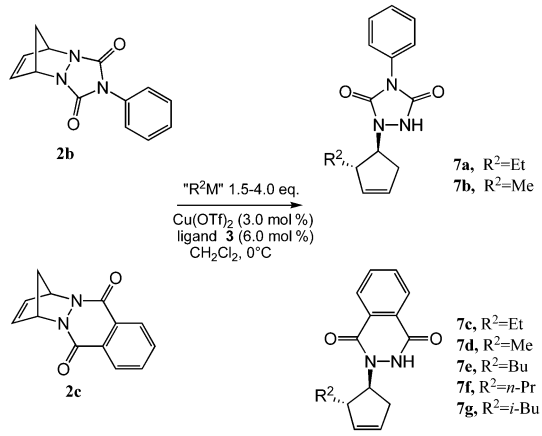
Despite the modest efficiency of the kinetic resolution, the results obtained with oxazabicyclic compounds were encouraging, and we considered symmetrical bicyclic hydrazines for a possibly even more appealing desymmetrization reaction with carbon nucleophiles. The addition of carbon nucleophiles to bicyclic hydrazines is an almost unexplored area. The palladium-catalyzed addition of stabilized enolates [8] and a palladium-catalyzed hydroarylation [9] were described only recently, but the ring-opened products were obtained as racemates, and no example of asymmetric ring-opening reactions with organometallic reagents has been reported so far. Initial experiments devoted to a challenging desymmetrization reaction of the most simple symmetrical bicyclic hydrazines **2a** were focused on the use of dialkylzincs as the organometallic reagent, but the ring-opening reaction did not occur at all.

We turned our attention to the use of the more rigid, tri- or tetracyclic Diels–Alder adducts **2b** and **2c** [9]. With these substrates, the reaction of dialkylzincs in the presence of a copper phosphoramidite catalyst afforded the corresponding ring-opened products, the *trans*-disubstituted hydrazino cyclopentenes **7a**, **7c**, and **7e**, with complete regio- and anti-stereoselectivity, but these were obtained with a very low yield and in racemic form (Table 1, entries 1–3). Therefore, we decided to change the primary organometallic reagent from the poorly reactive dialkylzinc reagents to the more reactive organoaluminum ones [10].

The use of organoaluminum reagents in combination with chiral copper catalysts has been exploited by several research groups, including our own, for the asymmetric conjugate addition to enones and other α,β-unsaturated carbonyl compounds [11]. To our delight, with the use of trialkylaluminum the corresponding opening products **7** were obtained with high yields and good enantioselectivities (entries 4–7). In most cases, it was possible to obtain adducts **7a**–**g** in a pure state after a simple washing of the crude mixtures with hexanes to get rid of the chiral ligand. This reaction can be considered a new asymmetric formal hydrazido alkylation of cyclopentadiene. The nice results obtained with diazabicycloheptenes **2b,c** seem to indicate a clear dependance of the enantioselectivity on the nature of the aluminum organyl. The best enantioselectivities were obtained with Me_3Al, and by the use of the more sterically demanding $(i\text{-Bu})_3Al$, a reversal of the facial selectivity was even observed (entry 10). These facts support the notion that the structure of the active catalyst incorporates an AlR_3-dependent substrate *binding pocket* [12]. During our study on symmetrical cyclic hydrazines, we noticed an interesting effect on the absolute sense of induction by the use of different chiral ligands. The best enantioselectivities were obtained with phosphoramidite **3a**, which has the same chirality descriptor of the BINOL and amine part of the ligand. The more popular, diastereoisomeric ligand **3b** gave a lower ee of 64 %, but most importantly, it gave the opposite enantiomer, despite the same chirality of the BINOL part of the chiral ligand, indicating that it is the amine part of the chiral ligand that plays a major influence. It should be noted that this is an important exception to the normal trend always observed in the copper-conjugate addition of organozinc reagents to enones, in which it is the chirality of the binaphthol unit that imposes the absolute stereochemistry of the conjugate adduct.

To sum up, the induced ring-opening in conjunction with C–C bond formation gives for the first time a new catalytic access to new hetero-functionalized alkyl cyclopentenes in an enantioenriched form, working from cheap starting materials. Our new reaction protocol is also robust and practical because most reactions can be carried out entirely at 0 °C without the necessity of a cryostatic cooling apparatus and syringe pumps to introduce the organometallic reagent.

Table 1 Desymmetrization of polycyclic hydrazines **2b,c** with organometallic reagents (R-M).[a]



Entry	Substrate	R^2-M	Time (h)	Conv. (%)[b]	ee (%)[c]
1	**2b**	Et_2Zn	24	38	3
2	**2c**	Et_2Zn	6	22	0
3	**2c**	Bu_2Zn	6	34(18)	18
4	**2b**	Et_3Al	4	>98(80)	66(+)
5	**2b**	Me_3Al	1	>98(92)	80(+)
6	**2c**	Et_3Al	4	94(84)	78(+)
7	**2c**	Me_3Al	4	>98(90)	86(+)
8[d]	**2c**	Me_3Al	4	>98(80)	64(–)
9[e]	**2c**	$(n\text{-Pr})_3Al$	20	>98(60)	54(+)
10[e]	**2c**	$(i\text{-Bu})_3Al$	20	95(78)	14(–)

[a]Reactions entirely carried out at 0 °C with chiral ligand (*R*,*R*,*R*)-**3a**.
[b]Determined by ^{1}H NMR of the crude mixture. Yield of isolated product in parentheses.
[c]Determined by HPCL on a Daicel Chiralpack AD-H. Sign of optical rotation reported in parentheses.
[d]Reaction carried out with diastereoisomeric ligand (*R*,*S*,*S*)-**3b**.
[e]Reaction carried out up to room temperature.

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