

Divergent Reactions for Racemates: Catalytic, Enantioselective, and Regiodivergent Nitroso Diels–Alder Reactions**

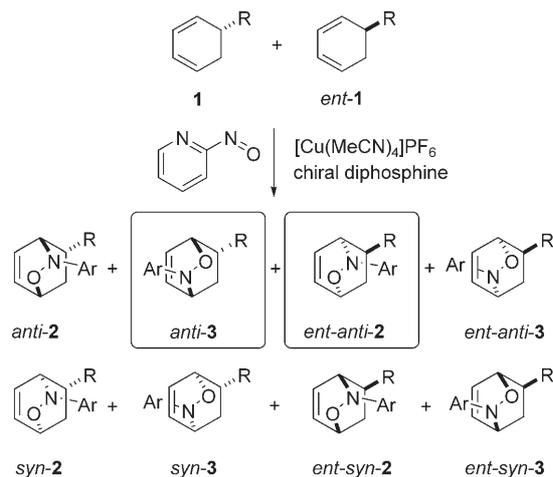
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Kinetic resolution of racemates is a widely used strategy for the synthesis of enantioenriched compounds.^[1] In the ideal case only one enantiomer reacts; hence, only half of the starting material is converted. However, in a parallel kinetic resolution both enantiomers are converted into non-enantiomeric products.^[1,2] According to Vedejs and Jure,^[1c] parallel kinetic resolution is a variation of a divergent reaction of a racemic mixture (divergent RRM) in which two complementary reagents or catalysts react with racemates leading to two non-enantiomeric products.^[1–3] However, in a divergent RRM a single catalyst or reagent reacts with racemates to give two distinct products with high enantioselectivity.^[1c] Herein we report on a divergent RRM in which racemic cyclohexadienes of type **1** undergo catalytic enantioselective nitroso Diels–Alder reactions to form the two major compounds *ent-anti-2* and *anti-3* (Scheme 1). In contrast to the other reported examples of divergent RRM^[3] in which the catalyst controls

the reaction giving four possible products, the present system deals with the selective formation of two products out of eight possible isomers!

To reduce the complexity of the system during catalyst screening we first studied the nitroso Diels–Alder reaction with the highly enantioenriched diene **1a** (R = (*S*)-CHPhOTBDPS (TBDPS = *tert*-butyldiphenylsilyl), 98% *ee*) readily obtained by our recently reported desymmetrization of 1,4-cyclohexadiene (the *ent* series in Scheme 1 can be neglected).^[4,5] The reactions were conducted in CH₂Cl₂ in the presence of [Cu(MeCN)₄]PF₆ (10 mol%), a chiral diphosphine (10 mol%) and 2-nitrosopyridine (–78 °C for 6 h then –20 °C for 12 h) to provide **2a** and **3a**. Cu^I catalysis has been shown by Y. and H. Yamamoto to be well suited for conducting nitroso Diels–Alder reactions.^[6] Ligands **4–8** were tested (among others), and the product ratio was determined by ¹H NMR spectroscopy (Table 1).^[7]

All the cycloadditions proceeded cleanly, and the products were isolated in quantitative combined yields. The



Scheme 1. All of the possible isomers that can be formed in the reaction of a racemic diene **1** with an aryl nitroso compound. R = phenyl, alkyl; Ar = 2-pyridyl

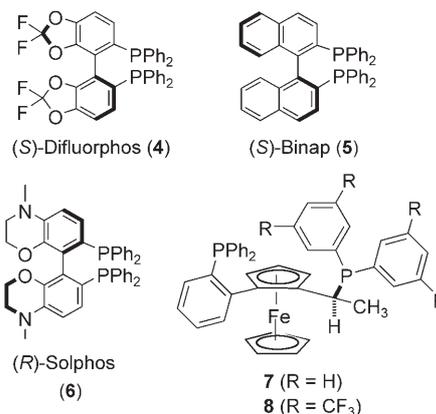


Table 1: Nitroso Diels–Alder reaction using different ligands and enantiomerically highly enriched **1a**.^[a]

Entry	Ligand	Ratio				
		<i>anti/syn</i>	<i>syn-2a</i> /	<i>syn-3a</i> /	<i>anti-2a</i> /	<i>anti-3a</i>
1	4	98:2	2	–	78	20
2	5	83:17	16	1	38	45
3	6	88:12	10	2	45	43
4	7	84:16	16	–	7	77
5	8	>99:1	–	–	2	98
6	<i>ent-8</i>	>99:1	–	–	95	5
7 ^[b]	8	>99:1	–	–	95 ^[c]	5 ^[d]

[a] Structures are given in Scheme 1 and Eq. (1) (R = (*S*)-CHPhOTBDPS, Ar = 2-pyridyl). [b] Reaction was performed with *ent-1* (R = (*R*)-CHPhOTBDPS). [c] Yield for *ent-anti-2a*. [d] Yield for *ent-anti-3a*.

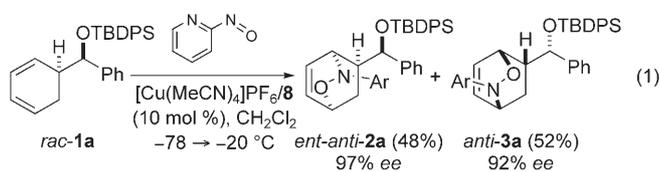
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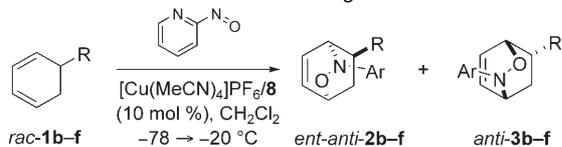
reaction with (*S*)-difluorophos (**4**)^[8a] as a ligand provided the adducts **2a** and **3a** with high diastereoselectivity (*anti/syn*=98:2; Table 1, entry 1). However, the regiochemistry for the *anti* isomers was not well controlled (78:20). Worse results were obtained with Binap^[8b] (Table 1, entry 2): both the *anti/syn* ratio and the regioselectivity for the major *anti* isomers were low. The reaction with (*R*)-Solphos (**6**)^[8c] afforded a similar result (Table 1, entry 3). The “walphos” ligand **7**^[8d] yielded the *anti* isomers **2a** and **3a** with good regioselectivity (1:11); however, only a moderate *anti/syn* selectivity was obtained (Table 1, entry 4). Pleasingly, excellent diastereo- and regioselectivity were achieved with the walphos ligand **8**^[8d] (Table 1, entry 5). Moreover, we found that with the enantiomeric ligand *ent*-**8** the regioselectivity could be reversed (Table 1, entry 6). As expected, high diastereoselectivity was obtained upon using *ent*-**8**. Thus it was not surprising that the enantiomeric diene *ent*-**1a** reacted with excellent selectivity under identical conditions with the walphos ligand **8** (Table 1, entry 7).

The stage was set for the study of the divergent nitroso Diels–Alder reaction of racemic diene **1a** [Eq. (1)]. The



products *ent-anti-2a* and *anti-3a* were isolated (column chromatography, SiO₂) in excellent combined yields and high enantiomeric excess.^[9] Other possible isomers were not identified. The nitroso Diels–Alder reaction was also tested with racemic dienes **1b–f** (Table 2). The reaction with **1b** occurred with excellent *anti/syn* selectivity to give *ent-anti-2b* and *anti-3b* with high enantioselectivities.^[9] Hence the additional chiral center in the substituent R of the test substrate **1a** does not influence the stereochemistry. The reaction with diene **1c** provided *ent-anti-2c* in 42% yield with excellent enantioselectivity (99% *ee*).^[9] The regioisomer *anti-3c* was isolated with 88% *ee* (45% yield).^[9] As compared to the other

Table 2: Nitroso Diels–Alder reaction using dienes **1b–e**.

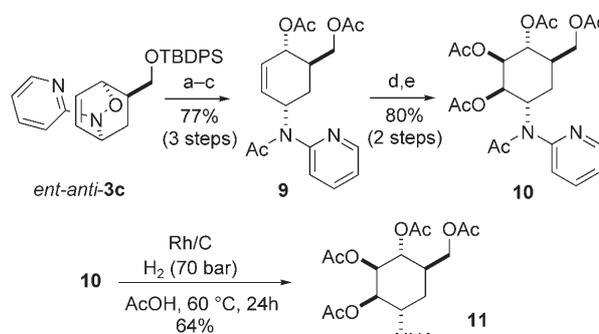


Diene	R	<i>ent-anti-2</i>		<i>anti-3</i>	
		Yield [%]	<i>ee</i> [%]	Yield [%]	<i>ee</i> [%]
1b	CMe ₂ OTMS ^[a]	48	95	52	89
1c ^[a]	CH ₂ OTBDPS	42	99	45	88
1d ^[b]	CH ₂ Ph	40	98	43	84
1e ^[c]	CH ₂ OAc	39	98	42	82
1f ^[d]	Ph	45	98	54	94

[a] One of the *syn* isomers, **2c** or **3c**, was formed in 13% yield. [b] The *syn* isomers **2d** and **3d** were formed in 17% combined yield. [c] The *syn* isomers **2e** and **3e** were formed in 19% combined yield. [d] The *syn* isomers were formed in trace amounts (< 1%). [e] TMS = trimethylsilyl.

substrates tested, the diastereoselectivity was lower for diene **1c** (*anti/syn* = 7:1). The smaller CH₂OTBDPS group does not effectively shield the *syn* face of the diene. Similar results were obtained for the benzyl-substituted diene **1d** and diene **1e** bearing an acyloxymethyl group showing that the silyloxy group is not required for high enantioselectivities. The best result was obtained for with Ph-substituted diene **1f**. For all dienes investigated, the *ent-anti-2* isomers are always formed in slightly lower yields but higher enantioselectivities than the *anti-3* adducts. Mechanistic studies on this divergent RRM are currently underway and will be reported in a full paper.

Finally we applied our new method to the synthesis of peracetylated 2-*epi*-validamine (**11**), which belongs to the class of pseudosugars or carbasugars with interesting biological activity.^[10] To this end the N–O bond in *ent-anti-3c* (89% *ee*),^[9] which is readily prepared from *rac-1c* with ligand *ent-8*, was cleaved using [Mo(CO)₆] and NaBH₄.^[11] Subsequent desilylation (TBAF) and acetylation gave cyclohexene **9** (Scheme 2). Diastereoselective OsO₄-catalyzed dihydroxylation and acetylation afforded the corresponding penta-acetylated carbasugar **10**. Cleavage of the 2-pyridyl group was



Scheme 2. a) [Mo(CO)₆], NaBH₄, MeOH/H₂O; b) TBAF, THF; c) 1. MeMgCl, THF; 2. AcCl; d) K₂OsO₂(OH)₄, NMO, acetone/H₂O; e) Ac₂O, pyridine. TBAF = tetrabutylammonium fluoride, NMO = 4-methylmorpholine *N*-oxide.

achieved by hydrogenolysis using H₂ and Rh/C^[12] to give **11** ([α]_D²⁵ = +16.5 deg cm³ g⁻¹ dm⁻¹, *c* = 12.6 mg cm⁻³, CHCl₃; [α]_D²⁵ = +18.0 deg cm³ g⁻¹ dm⁻¹, *c* = 11.0 mg cm⁻³, CHCl₃^[10b]).

In conclusion, we have developed a [CuPF₆(MeCN)₄]-catalyzed highly enantioselective regiodivergent nitroso Diels–Alder reaction. The starting dienes are readily available, and the products obtained are valuable compounds for the synthesis of biologically interesting carbasugars. We believe that divergent reactions on racemates can be observed for other Diels–Alder reactions of unsymmetrical dienophiles with racemic cyclic dienes. This might evolve to a general concept in the field of stereoselective cycloadditions. Work along this line is underway.

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