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Nordehydroabietyl amide-containing chiral diene for rhodium-catalysed asymmetric arylation to nitroolefins

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A highly enantioselective rhodium catalysed asymmetric arylation (RCAA) of nitroolefins with arylboronic acids is presented using a newly developed, C_1-symmetric, non-covalent interacted, phellandrene derived, nordehydroabietyl amide-containing chiral diene under mild conditions. Stereoelectronic effects were studied, suggesting an activation of the bound substrate through the secondary amide as a hydrogen-bond donor.

The rhodium-catalysed asymmetric arylation (RCAA) of organoboronic acids to electron-deficient olefins, pioneered by Miyaura and Hayashi,[1] is one of the most efficient methods for enantioselective C-C bond formation. In particular, excellent results were achieved using unsaturated carbonyl compounds.[2] Among the Michael acceptors,[3] nitroalkenes have been described as "synthetic chameleons"[4] because the optically versatile nitroalkanes obtained by RCAA can be transformed into a wide variety of optically active compounds such as α-substituted ketones[5] and biologically 2-arylethylamines,[6] which are useful chiral building blocks in protein kinase B (PKB) inhibitor,[6a] Telcagepant,[6b] and montanine-type *Amaryllidaceae* alkaloids bearing the cherylline synthon (Figure 1).[6c] Despite the great synthetic importance of optically active nitro compounds, RCAA to nitroolefins encountered the challenge by virtue of the difficulty in controlling the stereoselectivity and easily homocoupling of nitroalkanes under conventional basic conditions.[7] In 2000, Hayashi and co-workers discovered the first asymmetric addition to cyclic nitroalkenes using a Rh/BINAP catalyst,[5] followed by their impressive study on kinetic experiments on the 1,4-addition of phenylboronic acid to enones.[8]

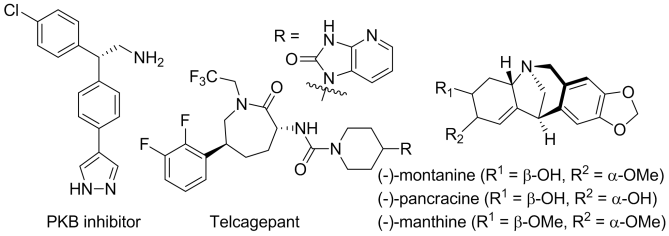

Figure 1. Biologically active 2,2-bisarylethylamines.

These studies indicate the catalyst turnover occurs much more rapidly with Rh/olefin than with analogous Rh/BINAP complexes. Therefore, C_2-symmetric bicyclo[3.3.0] dienes by Lin were established under harsh heating.[9a] This was followed by Wu's bicyclo[2.2.1]heptadiene,[9b] yet with the cost of its limited lifetime.[9c,d] Miscellaneous electron-deficient ligands were also developed, e.g., sulfinylphosphines,[10a] olefin sulfoxides,[10b] phosphoramidites,[10c] deoxycholic acid-derived phosphites.[10d] These hybrid ligands still possess some limitations, e.g., the sulfinyl moieties were mostly limited to *tert*-butyl substitution.

Inspired by Carreira's carvone derived diene[11] and Hayashi's phellandrene derived diene,[12] we thought a strategy is required: (1) to interact the catalyst with bound substrate close enough to facilitate reactions in an intramolecular fashion; (2) to introduce an extra chiral template and assist the stereospecific discrimination by stereoelectronic effects. From this point of view, the dienyl amide[13] with an additional hydrogen-bonding site represents an unmet need for further pursuit. Dehydroabietylamine and nordehydroabietylamine possess excellent structural backbones and well-defined contiguous stereocenters,[14] yet reports on their derivatives in asymmetric catalysis are scarce, mainly by virtue of poor asymmetric control due to distal manipulation of the bulky chiral template.[15a] Here, we make use of the unique hindrance of nordehydroabietyl amide to discriminate the prochiral face of nitroalkenes and developed a C_1-symmetric, hydrogen bonding interacted, phellandrene-derived, nordehydroabietyl amide-containing chiral diene that accomplishes RCAA of nitroolefins smoothly.

3a and **3f** are readily synthesized by amidation of α-phellandrene Diels-Alder derived dienyl carboxylic acid with optically pure dehydroabietylamine, and with nordehydroabietylamine,[15] respectively. The latter could be obtained by *Schmidt* reaction of dehydroabietic acyl azide derived from dehydroabietic acid.[15b,c] Whereas (*R*)-phellandrene is commercial available, the (*S*)-counterpart could be produced from Wilkinson's hydrogenation of (*R*)-carvone[16a] and Shapiro's olefination[16] sequentially on its hydrazone.

Conventional basic conditions[13] were first employed for RCAA to representative **1a** (Table 1). The addition of inorganic bases (entries 1-3) led to rapid decomposition of nitrostyrene with its homocoupl-

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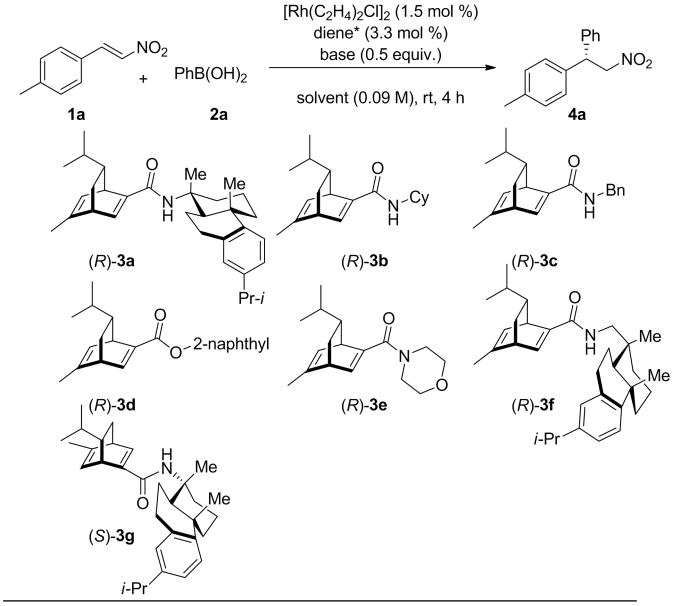
Table 1. Optimization of conditions.[a]



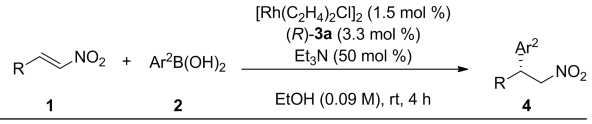
entry	diene	base	solvent	yield[b]	ee[c]
1	(*R*)-**3a**	NaOH	THF	0	N.D.[d]
2	(*R*)-**3a**	NaOH[e]	EtOH	23	89
3	(*R*)-**3a**	KF[e]	EtOH	40	74
4	(*R*)-**3a**	Pyridine	EtOH	N.R.[f]	N.D.[d]
5	(*R*)-**3a**	DABCO	EtOH	N.R.[f]	N.D.[d]
6	(*R*)-**3a**	DBU	EtOH	25	92
7	(*R*)-**3a**	Et_3N	toluene[g]	19	N.D.[d]
8	(*R*)-**3a**	Et_3N	THF[g]	trace	N.D.[d]
9	(*R*)-**3a**	Et_3N	CH_2Cl_2[g]	15	N.D.[d]
10	(*R*)-**3a**	Et_3N	EtOAc[g]	19	N.D.
11	**(*R*)-3a**	**Et_3N**	**EtOH**	**90**	**91**
12	(*R*)-**3a**	Et_3N	TFE[h]	N.R.[f]	N.D.[d]
13	(*R*)-**3a**	Et_3N	HOAc	N.R.[f]	N.D.[d]
14	(*R*)-**3b**	Et_3N	EtOH	53	76
15	(*R*)-**3c**	Et_3N	EtOH	84	56
16	(*R*)-**3d**	Et_3N	EtOH	97	71
17	(*R*)-**3e**	Et_3N	EtOH	88	1
18	(*R*)-**3f**	Et_3N	EtOH	97	80
19	(*S*)-**3g**	Et_3N	EtOH	86	-92

[a] The reaction was carried out with nitro-*p*-Me-styrene **1a** (0.36 mmol), $PhB(OH)_2$ (0.9 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), diene **3*** (3.3 mol %), and corresponding base (0.18 mmol) in solvent (4 mL) at room temperature under N_2 for 4 h; [b] Isolated yield; [c] Enantiomeric excesses were determined by chiral HPLC analysis; [d] Not determined; [e] Corresponding inorganic base (1.5 M) in 0.12 mL H_2O; [f] No reaction; [g] 8 h; [h] TFE = trifluoroethanol.

ing adduct being observed (entry 1), yet with a slight impact on the satisfying enantioselectivity. This indicates a milder base is needed to release rhodium nitronate slowly. However, rigid or bulky amines still have a detrimental effect on the conversion (entries 4-7). Another concern is that hydrolysis of a rhodium nitronate in donating solvents could reduce polymerization. Next we conducted control experiments involving non-polar, polar aprotic, and polar protic solvents (entries 7-13). Gratifyingly, solvents show a crucial effect in increasing both the reaction rate and conversion. We thought a stronger protic solvent may benefit the reaction. However, the effect of the acids CF_3CH_2OH and HOAc (entries 12 and 13), used as solvents, is mainly to neutralize triethyl amine and, as a consequence, the reaction does not work. Finally, EtOH was proven to be the best solvent in good conversion (yield 90%), promising 91% ee value ((*S*)-product as the major enantiomer) and shortened time (entry 11); Therefore, with Et_3N in EtOH as the best condition, a variety of chiral dienes were prepared and assessed to explore further the stereoelectronic effects of (*R*)-**3a** analogues. Dienes lacking hydrogen bonding were tested first, among which, Hayashi's **3d**[12b] with a 2-naphthyl ester noticeably afforded an excellent yield (entry 16). However, enantioselectivity dropped to 71%. Lam's **3e**[13a] tertiary amide was obviously inferior by affording the racemic product (entry 17). By contrast, hydrogen-bond donors **3b** and **3c**[13d], lacking chiral centers on the cyclohexane and the benzyl group, respectively, provided **4a** in moderate ees, with the yields somewhat diminished (entries 14 and 15). This demonstrates that the performance of dienes bearing secondary amides are better than those otherwise, indicating amides' hydrogen bonds are capable of interacting with nitrostyrene during the process of stereochemical induction. To bind closer to the substrate, we wanted to reduce the steric hinderance of the amide by linking the diene to dehydroabietyl amide fragment, where the constrained quaternary carbon was no longer adjacent to N-H bond. (*R*)-**3f** did offer an outstanding yield, nonetheless accompanied by losing some degree of enantioselectivity (entry 18). This steric effect is intriguing. It illustrates that sterically encumbering nordehydroabietyl amide is essential to sustain the high efficiency of enantioselection. What is more, we intended to find out if the additional chiral template was a matched combination[9d,13a] with the (*R*)-diene, so we synthesized the diastereomeric ligand by connecting nordehydroabietyl amide scaffold with (*S*)-phellandrene derived diene and applied it into RCAA correspondingly. As a matter of fact, (*S*)-**3g** offered a preference of the (*R*)-product with a slightly inferior yield (86%), yet with similar ee value as that of (*R*)-**3a** (entry 19). It shows a weak matched-mismatched effect, implying the asymmetric induction is mainly determined by the absolute configuration of the diene fragment. On the other hand, hydrogen bonds from secondary amides presumably promote non-covalent interactions with nitrostyrene, thus enhancing both enantioselectivities and bridging the gap of matched and mismatched effects on the outcome of the reaction.[17] Another factor is likely to be attributed to the steric effect of the appreciably bulky nordehydroabietyl amide,[18] distinguishing prochiral faces (*Re*/*Si*) through arylrhodation of the bound substrate, has outcompeted the mismatched effect of two chiral templates.[13d]

On the basis of these results, the condition in entry 11 of Table 1 was selected to explore the scope of nitroalkenes with various arylboronic acids (Table 2). A range of arylboronic acids

Table 2. Asymmetric conjugate addition to linear nitroalkenes.[a]



1 2 4

entry	R	Ar^2	4	yield[b]	ee[c]
1	4-MeC_6H_4	2-MeC_6H_4	**4b**	95	94
2	4-MeC_6H_4	4-FC_6H_4	**4c**	78	93
3	4-MeC_6H_4	4-ClC_6H_4	**4d**	58	95
4	4-MeC_6H_4	4-BrC_6H_4	**4e**	83	93
5	4-MeC_6H_4	4-$MeOC_6H_4$	**4f**	99	46
6	4-MeC_6H_4	4-$BnOC_6H_4$	**4g**	98	77
7	4-MeC_6H_4	4-*t*-BuC_6H_4	**4h**	64	90
8	4-MeC_6H_4	1-Np[d]	**4i**	93	98
9	4-MeC_6H_4	2-Np[d]	**4j**	91	84
10	4-MeC_6H_4	biphenyl-4	**4k**	93	81
11	4-$MeOC_6H_4$	Ph	**4l**	97	85
12[e]	4-$Me_2NC_6H_4$	Ph	**4m**	52	96
13[e]	3,4-diMeOC_6H_4	Ph	**4n**	64	97
14	4-FC_6H_4	Ph	**4o**	83	73
15	4-ClC_6H_4	Ph	**4p**	96	86
16	*n*-Bu	Ph	**4q**	64	61
17	Ph	4-BrC_6H_4	**4r**	91	82

[a] The reaction was carried out on a 0.36 mmol scale nitroolefin with 2.5 equiv of arylboronic acid, $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), (*R*)-**3a** (3.3 mol %), and 0.5 equiv of Et_3N in ethanol at room temperature for 4 h under nitrogen atmosphere; [b] Yield of isolated product; [c] Enantiomeric excesses were determined by chiral HPLC analysis; [d] Np = naphthyl; [e] heating at 50 °C for 8 h.

that gave arylation products with moderate to high yields and ee values are electron-rich ones, including 2-Me (entry 1), 4-OMe (entry 5) and 4-BnO (entry 6) analogues. The electron-withdrawing substituents on the arylboronic acids were also tolerated (entries 2-4, and 17), and the performance of bulky ones (entries 7-10) is also effective in conversion and stereochemical induction. For nitrostyrene scope, the ones bearing strong electron-donating groups (entries 12 and 13) are a bit sluggish and need heating (52% and 64%, respectively). An aliphatic nitroalkene (entry 16) also proved to be reactive under the current protocol, yielding a moderate 64% yield and 61% ee. The absolute configuration of representative **4e** was confirmed by X-ray crystallography (Figure 2).

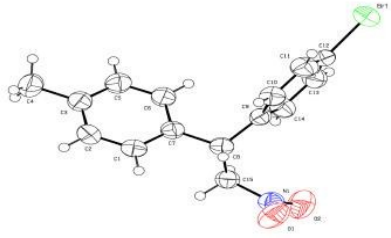
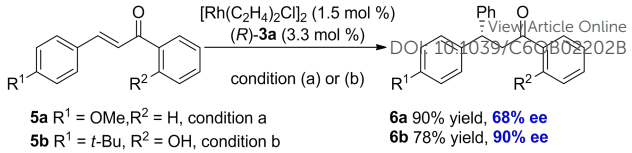


Figure 2. X-ray crystal structure of **4e**
(displacement ellipsoids are drawn at the 45% probability level).

To illustrate the practicability of current protocol, (*R*)-**3a** was applied to RCAA of an electron-rich chalcone and a phenoxy alternative. Compared with conventional inorganic basic conditions, asymmetric 1,4-adducts were also obtained in gratifying yields with good ees (Scheme 1).



5a R^1 = OMe,R^2 = H, condition a
5b R^1 = *t*-Bu, R^2 = OH, condition b

6a 90% yield, **68% ee**
6b 78% yield, **90% ee**

condition (a) $PhB(OH)_2$ (2.5 equiv.), Et_3N (0.5 equiv.), EtOH, 70 °C, 5 h; (b) Ph_4BNa (1 equiv.), 1,4-dioxane, 80 °C, 4 h.

Scheme 1. 1,4-Asymmetric addition to chalcones.

Based on the aforementioned process, a model was postulated that explains the stereochemical outcome of the addition reaction (Figure 3). The coordination mode mainly depends on the size of nordehydroabietyl amide. The interaction of nitroolefins to diene-Rh-Ar occurs in a *Si*-face manner to minimize unfavorable steric repulsion between nitroalkenes and the amide moiety. In addition, EtOH is believed to act as a hydrogen bond linker that helps the secondary amide as a hydrogen bond donor closer to the nitro group, thus greatly accelerating the addition.

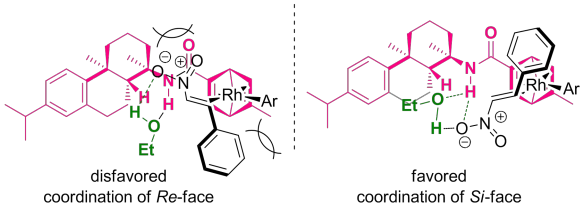
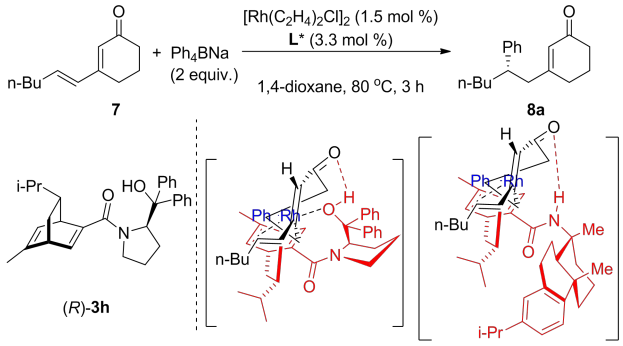


Figure 3. A model for stereochemical induction.

Although rhodium-catalysed conjugate addition has been developing rapidly, only a few examples of asymmetric 1,6-additions to dienones have been reported by a chiral bisphosphine-rhodium catalyst.[19] This may be ascribed to the considerable difficulty in controlling regioselectivity of the addition to extended conjugate systems. The phenylboronic acid displayed no nucleophilic activity, then the use of aryl zinc[19a] and aryltitanate reagents[19b] in the presence of chlorotrimethylsilane followed by acidic hydrolysis does not offer a practical access to chiral 1,6-regioselective addition to α,β,γ,δ-unsaturated carbonyl compounds. During our efforts to realize 1,6-addition to cyclic dienones, we found the ligands without hydrogen bonding interaction, or lacking nordehydroabietyl amide moiety albeit with hydrogen bonding, led to low conversions and inferior ee values (Table 3, entries 3, 4, 6-9). In contrast, (*R*)-**3a**, or an alternative (*R*)-**3h**, gave exclusively 1,6-addition product **8a** in high yields with satisfying enantioselectivities upon the addition of sodium tetraphenyl boron to cyclic dienones at milder heating 50 ℃ (Table 3, entries 5 and 10).[19] In our proposed Rh/diene-dienone interacted model, the free hydroxyl group from (*R*)-**3h** presumably binds to carbonyl of dienone *via* hydrogen-bond interaction, as also existed in nordehydroabietyl amide moiety in (*R*)-**3a**, thus approaches the substrate close enough to facilitate RCAA's conversion at a less bulky δ-position. The control experiment is of evidence, supporting hydrogen-bond interaction crucial in determining prominent facial discrimination.

Table 3. Regioselective 1,6-asymmetric addition.[20]



entry	L* (*R*)-	T	yield (%)[a]	ee (%)
1	**3a**	80	94	35
2	**3a**	80	-[b]	-
3	**3d**	80	26	15
4	**3f**	80	28	9
5	**3a**	50[c]	93	91
6	**3b**	50[c]	69	81
7	**3c**	50[c]	28	41
8	**3d**	50[c]	4	56
9	**3e**	50[c]	69	83
10	**3h**	50[c]	87	93

[a] isolated yield after 3 h at 80 °C, unless otherwise specified; brsm = based on starting matierial's yield; [b] upon addition of TMSCl (1 equiv.), incomplete conversion after 7 h stirring; [c] 16 h.

Conclusions

In summary, we have developed a low-loading rhodium-nordehydroabietyl amide-containing chiral diene catalysed conjugate arylation to nitroalkenes in high yield and ee. The work exemplifies the capacity of nordehydroabietyl amide moiety containing a unique hindrance and non-covalent interaction with electron-deficient olefins, which was evident and further illustrated in 1,6-site-selective rhodium-chiral diene catalysed asymmetric arylation of dienone.

Acknowledgements

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