Hydroboration

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Asymmetric Hydroboration of 1,1-Disubstituted Alkenes**

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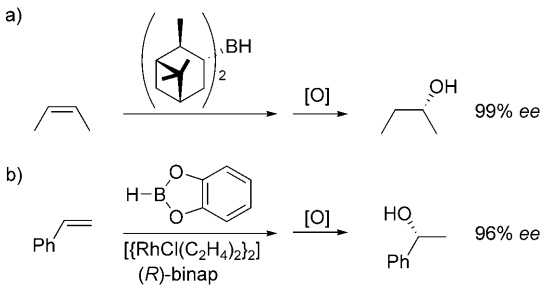
alkenes · asymmetric synthesis · enantioselectivity · hydroboration

H. C. Brown's dramatic enantioselectivities observed in the hydroboration of alkenes in 1961 using (−)-diisopinocampheylborane [(Ipc)$_2$BH] heralded the birth of asymmetric synthesis (Scheme 1a).[1] He showed for the first time that simple chiral reagents of low molecular weight were capable of inducing levels of enantioselectivity that hitherto belonged exclusively to the domain of enzymes.



Scheme 1. Asymmetric hydroboration reactions. binap = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl.

Since this landmark discovery, a large number of chiral hydroborating agents and catalysts have been developed,[2] but the original reagents (Ipc)$_2$BH and (Ipc)BH$_2$ remain widely used. They usually give good to high enantioselectivities with a broad range of alkenes (Table 1, columns 2 and 3).[3] Whilst Masamune's C_2-symmetric borane (2,5-dimethylborolane, DMB) gives higher enantioselectivities in the majority of cases (Table 1, column 4),[4] its lengthy synthesis (7 steps) detracts from the practicality of using this reagent relative to that of Brown's.

In recent years rhodium-catalyzed hydroboration has been developed, a process which usually gives complementary regioselectivity to the uncatalyzed process. Furthermore, by using chiral ligands high enantioselectivity has been achieved (Scheme 1b).[5]

Table 1: Enantioselectivities obtained in the hydroboration of different classes of alkenes.

Alkene class	(Ipc)$_2$BH	(Ipc)BH$_2$	DMB	5a	5b
	14	73	99.5	96	95
	99.1	24	97.6	32	84
	15	53	97.6	74	–
iPr	32	–	1.5	38	52
Ph	–	5	–	78	66

The enantioselectivities observed in the hydroboration of different classes of alkenes with selected chiral reagents are summarized in Table 1. It is clear, and perhaps unsurprising, that one class of alkenes stands out as being especially challenging: 1,1-disubstituted alkenes. It is difficult for a chiral reagent to effectively distinguish between the two enantiotopic faces of such substrates since they are *barely* prochiral. Indeed, achieving high enantioselectivity in the transformations of 1,1-disubstituted alkenes represents the ultimate challenge in asymmetric synthesis. (H. C.) Brown's hydroboration[4] and (J. M.) Brown–Hayashi's rhodium-catalyzed hydroboration[5b] gave low selectivities (Table 2, entries 1 and 2). The Jacobsen–Katsuki[6] and Shi[7] epoxidations gave higher enantioselectivities, which are now approaching practical levels (Table 2, entries 3 and 4). Until recently, only asymmetric hydrogenation and dihydroxylation reactions had provided more than 90% *ee* (Table 2, entries 5 and 6). Sharpless asymmetric dihydroxylation was found to give very high enantioselectivities with both 1,1-arylalkyl- and 1,1-dialkylethenes (Table 2, entry 5).[8] Pfaltz and Andersson have independently reported that chiral iridium-based catalysts were highly effective for the hydrogenation of 1,1-disubstituted alkenes (Table 2, entry 6), as well as other substitution patterns.[9]

Asymmetric hydrogenation and dihydroxylation usually give exceptionally high enantioselectivities over a broad

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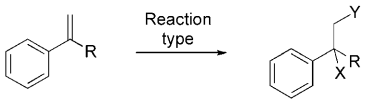
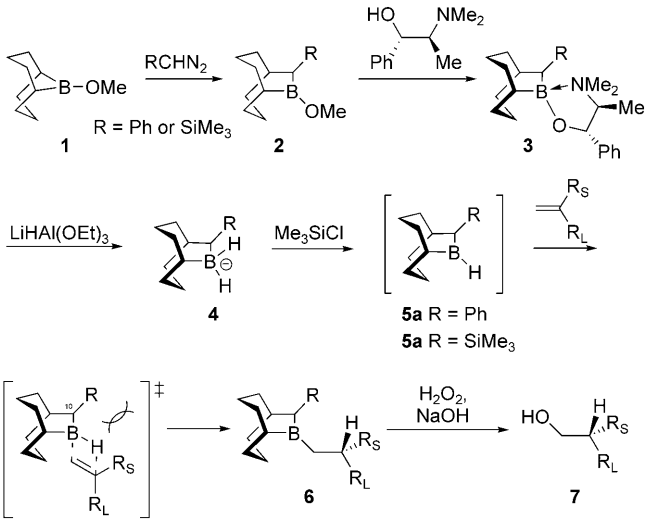
Table 2: Asymmetric transformations of 1,1-disubstituted arylalkylethenes.



Entry	Reaction type	Product X, Y	*ee* [%]	Ref.
1	Hydroboration [(Ipc)$_2$BH/(Ipc)BH$_2$]	H, OH	<5	[4]
2	Hydroboration [Rh catalyst]	H, OH	38–47	[5]
3	Epoxidation [Mn–salen complex]	-O-	54	[6]
4	Epoxidation [ketone catalyst]	-O-	62–88	[7]
5	Dihydroxylation [Os–amine catalyst]	OH, OH	94–96	[8]
6	Hydrogenation [Ir–phosphine catalyst]	H, H	94–99	[9]

range of substrates, including 1,1-disubstituted alkenes, and so they pass the ultimate test. Soderquist has now shown that a new class of hydroborating agents **5a** and **5b** are uniquely effective for 1,1-disubstituted alkenes, now passing the ultimate test.[10] The 10-substituted-9-borabicyclo-[3.3.2]decane scaffold had previously been used in highly effective allyl- and crotylboration of aldehydes and ketones (81–99% *ee*).[11] The basic scaffold of these reagents was prepared in enantiopure form by ring expansion of *B*-methoxy-9-BBN (**1**) and resolution of **2** to **3**, followed by reduction to give the borohydride derivatives **4** (Scheme 2). Hydroboration reactions were subsequently carried out in the presence of one equivalent of Me_3SiCl to generate the reactive boranes **5** in situ (Scheme 2).

In the hydroboration of a range of alkenes, reagents **5a** and **5b** outperform Brown's reagents (Table 1, compare columns 5 and 6 with 2 and 3), but not Masamune's (Table 1, column 4).[4,10] However, it is in the hydroboration of 1,1-disubstituted alkenes that Soderquist's reagents really stand out (Table 1, rows 4 and 5 and Table 3). Whereas previously enantioselectivities rarely rose above 10% *ee*, the new reagents give up to 92% *ee*.

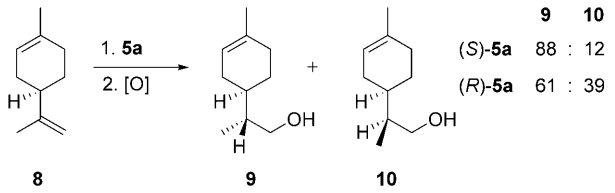


Scheme 2. Synthesis and use of **5a** and **5b** in the hydroboration of 1,1-disubstituted alkenes.

Table 3: Hydroboration of 1,1-disubstituted alkenes using reagents **5a** and **5b**.

Entry	Alkene	Reagent	*ee* [%]	Yield [%]
1	Et	**5a**	28	83
		5b	**40**	87
2	*i*Pr	**5a**	38	97
		5b	**52**	82
3	*t*Bu	**5a**	**92**	84
		5b	56	60
4	Ph	**5a**	**78**	95
		5b	66	83

Reagent (*S*)-**5a** was also effective in the hydroboration of (*R*)-limonene (**8**) giving the highest selectivity to date for this substrate (d.r. 88:12; Scheme 3). The mismatched combination gave a 61:39 ratio of diastereoisomers in favor of the same major diastereoisomer as that observed when (*S*)-**5a** was used, indicating a significant degree of substrate control.

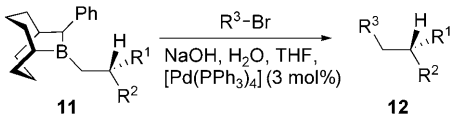


Scheme 3. Diastereoselective hydroboration of (*R*)-limonene (**8**).

Steric factors are believed to be primarily responsible for controlling the outcome of the reaction. The alkene approaches from the opposite side of the C10 substituent such that the larger alkene substituent is remote from it (transition-state structure in Scheme 2). The nature of the 10-substituent also influences the conformation of the bicycle which subtly influences selectivity in both the hydroboration and allyl/crotylboration reactions.[11]

The intermediate trialkylboranes **11** have also been used as coupling partners in Suzuki–Miyaura reactions with aryl-, heteroaryl-, and vinylbromides thereby extending the utility of the current process (Scheme 4). Compounds **12**, where R^1 and R^2 = aryl/heteroaryl represent important pharmacophores in medicinal chemistry which are not easy to prepare in an enantioenriched form.[12] It remains to be seen whether 1,1-diarylsubstituted ethenes will succumb to effective asymmetric hydroboration reactions to fill this methodological gap.

In recent years there has been a resurgence of interest in the field of organoboron chemistry with new reactions and new catalytic processes emerging. Hydroboration is one of the oldest of the reactions in the field and the work of Soderquist and co-workers on the hydroboration of 1,1-disubstituted



Scheme 4. Suzuki–Miyaura coupling reaction of borane intermediates.

alkenes, the most challenging of substrates, represents a significant milestone in its continued development. Additional improvements in enantioselectivity and ease of access to the hydroborating agents are still required to bring the hydroboration reaction into the class of reactions which are routinely used with confidence for all classes of alkene.

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