

CHIRAL FLEXIBILITY IN INSECT PHEROMONES: WHY DO SOME SPECIES
TOLERATE THE WRONG STEREOISOMER?

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Abstract—Many insect pheromones are chiral, and receivers respond to non-natural stereoisomers in strikingly different ways: some are completely inhibited by a few per cent of the antipode, some ignore it, some require both enantiomers, and at least one responds more strongly to stereoisomers it does not produce. These response types were catalogued two decades ago, and the most common of them, a non-natural enantiomer that neither attracts nor inhibits, was recognised as allowing racemic lures in practice. What remains unclear is why a given species falls into one response type rather than another. We define chiral flexibility as behavioural tolerance of, or dependence on, stereoisomers other than the natural one, distinguish it from failure to detect the antipode, and reassemble the evidence across Coleoptera, Hemiptera and Lepidoptera. We then evaluate three classes of explanation. First, receptor architecture: broadly and narrowly tuned receptors coexist in the same antenna, and behavioural fidelity is weighted centrally rather than fixed at the periphery. Second, biosynthesis: in stink bugs the terpene

synthase is stereospecific while the natural stereoisomeric blend is set by later steps, and in termites a single amino acid substitution shifts the enantiomeric composition of an enzyme's product. Third, community context: fidelity is often, though not always, tight where a synchronously active species uses the antipode. We examine methodological artefacts that can mimic flexibility, show that the cost of enantiopure lures depends on whether plants supply the insect's configuration, and propose comparative tests within clades.

Key Words: Chirality, enantiomer, Heteroptera, odorant receptor, pheromone, terpene synthase.

INTRODUCTION

Chirality pervades insect pheromones. Since the first enantioselective syntheses of the 1970s made pure stereoisomers available for bioassay, the relationship between absolute configuration and bioactivity has been studied in well over a hundred species. Mori (2007) reviewed about 140 chiral pheromones and classified their stereochemistry–bioactivity relationships into ten categories. These range from a single active enantiomer whose antipode does not inhibit, through antipodal inhibition, to cases in which both enantiomers are required, or a mixture outperforms the single enantiomer. The first category was the most common, accounting for about 60% of the pheromones reviewed, and Mori noted that pheromones in this category can be used as racemates in practical applications.

Mori's categories describe what receivers do. The categories do not explain why a given species falls into one category rather than another, and the prospects Mori outlined concerned analytical methods rather than causes. The only causal remark in that review attributes the weak activity of the natural German cockroach pheromone stereoisomer to biosynthetic restriction (see below). Sims et al. (2022) reviewed enantiomeric discrimination by odorant-binding proteins and odorant receptors. They found few clear examples of discrimination by these peripheral proteins,

noted that some receptors respond to several enantiomers of a pheromone component, and recommended that binding and receptor studies include both enantiomers of chiral ligands. Although their review addressed the molecular capacity for discrimination, why behavioural responses to stereoisomers differ among species was outside its scope.

The applied literature on stink bugs has meanwhile adopted the word *flexibility*. Leskey et al. (2015) concluded that attraction to non-pheromonal stereoisomers, and the absence of inhibition by them, increase the flexibility of developing pheromone products for the brown marmorated stink bug, *Halyomorpha halys*. Weber et al. (2020) likewise described the insensitivity of *H. halys* to component ratios as giving flexibility for cost-efficient synthesis. In both cases the word *flexibility* refers to lure manufacture. Here we use *chiral flexibility* for a property of the signalling system itself. A species shows chiral flexibility when (i) adding a non-natural stereoisomer to the natural pheromone at a biologically relevant proportion does not reduce the behavioural response, (ii) a mixture of stereoisomers is as active as, or more active than, the natural composition, or (iii) the response requires more than one stereoisomer. We distinguish this from *inertness*, in which the antipode is barely detected at the antenna and has no behavioural effect (Dickens and Mori 1989). Tolerating a stereoisomer that is detected and failing to detect it at all are different phenomena, and they are likely to have different explanations.

This review argues that (i) receiver responses to stereoisomers are taxonomically and ecologically patterned rather than noise, once methodological artefacts are excluded; (ii) the pattern has identifiable receptor-level, biosynthetic and ecological explanations; (iii) it has economic consequences for lure production; and (iv) it has never been tested comparatively within a clade, which is the principal gap.

A FRAMEWORK FOR RECEIVER RESPONSES TO STEREOISOMERS

Table 1 groups the cases discussed in this review by the behavioural effect of the non-natural stereoisomer, with the corresponding category of Mori (2007). Two departures from Mori's scheme are deliberate. First, Mori's most common category, a single active enantiomer with a non-inhibitory antipode, combines two situations that electrophysiology can separate: an antipode that is not detected (inert) and one that is detected but behaviourally neutral (tolerated). Second, we list separately cases in which the natural stereoisomer is unknown, because tolerance of an unnatural stereoisomer cannot be assessed without knowing which one is natural.

TABLE 1 BEHAVIOURAL RESPONSES OF RECEIVERS TO NON-NATURAL STEREOISOMERS OF THEIR PHEROMONES, GROUPED BY RESPONSE TYPE AND MAPPED ONTO THE CATEGORIES OF MORI (2007)

Response of receiver to non-natural stereoisomer	Mori (2007) ^a	Examples (compound; key observation)	Sources
A. Antagonistic: small proportions abolish response	4.2	<i>Anomala osakana</i> ((S)-japonilure; 5% (R) completely inhibited field catches); <i>Popillia japonica</i> and <i>A. corpulenta</i> ((R)-japonilure; (S) antagonistic); Californian and Idaho <i>Ips pini</i> ((-)-ipsdienol; about 5% (+) virtually eliminated attraction); <i>Gnathotrichus retusus</i> ((S)-sulcatol; no response above 2% (R)); <i>Agriopsis aurantiaria</i> ((3S,4R)-epoxide); <i>Lymantria dispar</i> ((+)-disparlure)	Leal 1996; Wang et al. 2026; Birch et al. 1980; Lanier et al. 1980; Borden et al. 1980; Szöcs et al. 1993; Vité et al. 1976
B. Reduced but not abolished	4.2 (partial)	<i>Colotois pennaria</i> and <i>Erannis defoliaria</i> (opposite enantiomers of (3Z,9Z)-6,7-epoxynonadecadiene; racemate caught significantly fewer males)	Szöcs et al. 1993
C. Inert: antipode barely detected and behaviourally neutral ^b	4.1	<i>Anthonomus grandis</i> ((+)-grandisol; EAG threshold 100–1000× higher for (-); no significant inhibition in the field); <i>Lymantria monacha</i> ((+)-disparlure; unaffected by (-); no antennal sensitivity to (-))	Dickens and Mori 1989; Klimetzek et al. 1976; Hansen 1984
D. Tolerated: detected, behaviourally neutral at relevant proportions ^b	4.1	<i>Agriopsis marginaria</i> (attractant (6S,7R)-epoxide; antipode no effect despite strongest EAG discrimination); <i>Ips calligraphus</i> ((S)-cis-verbenol; (R) neutral at comparable amounts, suppressive at ≥10×); <i>Halyomorpha halys</i> (unnatural stereoisomers not inhibitory; captures insensitive to minor stereoisomer)	Szöcs et al. 1993; Vité et al. 1976; Khrimian et al. 2014b; Leskey et al. 2015; Weber et al. 2020
E. Both required; broad ratio plateau	4.7, 4.5	<i>Gnathotrichus sulcatus</i> ((S)-(+):(R)-(-)-sulcatol produced at 65:35; neither enantiomer active alone; no difference among stimuli with ≥25% of either); New York <i>I. pini</i> ((+):(-)-ipsdienol produced at 65:35; field optimum 50:50); Wisconsin and Michigan <i>I. pini</i> ((+):(-)-ipsdienol blends from 25:75 to 75:25 all attractive)	Byrne et al. 1974; Borden et al. 1976, 1980; Lanier et al. 1980; Herms et al. 1991
F. Synergistic: antipode inactive alone but enhances response	4.8	<i>Acanthoscelides obtectus</i> ((R)-methyl 2,4,5-tetradecatrienoate; equal (S) enhanced preference, ≤10% (S) no effect)	Mohan-Kumar et al. 2025

Response of receiver to non-natural stereoisomer	Mori (2007) ^a	Examples (compound; key observation)	Sources
G. Non-natural stereoisomers more active than natural	3.4	<i>Blattella germanica</i> ((3 <i>S</i> ,11 <i>S</i>)-3,11-dimethylnonacosan-2-one least active of four stereoisomers)	Eliyahu et al. 2004; Mori 2007
H. Unresolved: natural configuration unknown	—	<i>B. germanica</i> (3,11-dimethylnonacosane; all four stereoisomers active, (3 <i>S</i> ,11 <i>S</i>) most active); <i>Dolycoris baccarum</i> ((±)-α-bisabolol attractive but less so than live males)	Zhou et al. 2026; Yang et al. 2019

^a Section numbers of the stereochemistry–bioactivity categories in Mori (2007)

^b Categories C and D both fall within Mori's category 4.1; they are distinguished here by electrophysiological evidence of whether the antipode is detected

Two features of Table 1 frame the rest of the review. Strict antagonism and relaxed fidelity occur within the same genera (*Ips*, *Gnathotrichus* and *Agriopsis* and its relatives) and even within one species (*Ips pini*). The pattern is therefore not a property of high-rank taxa. In addition, the distinction between inert and tolerated antipodes has been tested electrophysiologically in only a handful of species.

STRICT FIDELITY: WHERE THE ANTIPODE MATTERS

The cases that established the importance of stereochemistry are robust, and they remain the benchmark against which flexibility must be measured. Females of the Osaka beetle, *Anomala osakana*, produce (*S,Z*)-5-(1-decenyl)oxacyclopentan-2-one [(*S*)-japonilure]. In field tests, catches in traps baited with the (*S*)-enantiomer were completely inhibited by adding only 5% of the (*R*)-enantiomer, and the (*R*)-enantiomer alone did not differ from unbaited traps (Leal 1996). The Japanese beetle, *Popillia japonica*, uses the same compound with the roles reversed: it produces and responds to (*R*)-japonilure and is inhibited by (*S*) (Leal 1996). The copper green chafer, *A. corpulenta*, also uses (*R*)-japonilure, with (*S*) acting as a behavioural antagonist (Wang et al. 2026).

Bark beetles provide parallel cases. In California, *Ips pini* did not respond to synthetic racemic ipsdienol in the laboratory or field, whereas (–)-ipsdienol, the naturally produced

enantiomer, was as attractive as males boring in ponderosa pine. The (+)-enantiomer interrupted the response to a natural source, and ipsdienol containing only 5% of (+) was virtually inactive (Birch et al. 1980). (+)-Ipsdienol is a pheromone component of the competing species *I. paraconfusus* (Vité et al. 1978). Idaho *I. pini* likewise produces (–)-ipsdienol, and its laboratory response to it is inhibited by (+)-ipsdienol (Lanier et al. 1980). The ambrosia beetle *Gnathotrichus retusus* produces at least 99% optically pure (*S*)-sulcatol. Its females responded to (*S*)-sulcatol of 100, 99 and 98% purity but not to mixtures containing more than 2% of the (*R*)-enantiomer, and racemic sulcatol was unattractive (Borden et al. 1980).

Among moths, male gypsy moths (*Lymantria dispar*, reported as *Porthetria dispar*) responded in large numbers to (+)-disparlure but only in low numbers to (–)-disparlure or to both enantiomers together, and the inhibitory effect increased with the proportion of (–) (Vité et al. 1976). In the geometrid *Agriopis aurantiaria*, the antipode of the natural (3*S*,4*R*)-epoxynonadecadiene caught no males and drastically reduced catches when added to the natural enantiomer (Szöcs et al. 1993).

These cases share a feature: in most, a sympatric species, or another population of the same species, uses the antipode. We return to this under Community Context. They are the most often cited cases, but by Mori's (2007) tally, they are not the most common response type.

RELAXED FIDELITY: THE COUNTER-CASES

Heteroptera. Stink bugs provide the most extensively documented cluster of relaxed fidelity cases. Souza et al. (2025) compiled the chemical compounds reported for nearly ninety pentatomid taxa, including sex and aggregation pheromones for 53 species, and used pheromone characters to infer the phylogenetic position of three species. The chemical ecology of *H. halys* has been reviewed by Weber et al. (2017). Many of these pheromones are stereochemically

complex bisabolane sesquiterpenes, and this complexity forced researchers to test stereoisomeric mixtures. Khrimian et al. (2014b) developed a rhodium-catalysed asymmetric route to all stereoisomers of 1,10-bisaboladien-3-ol and 10,11-epoxy-1-bisabolen-3-ol, confirming configurations by X-ray crystallography. Using enantioselective GC, they identified (3*S*,6*S*,7*R*,10*S*)- and (3*R*,6*S*,7*R*,10*S*)-10,11-epoxy-1-bisabolen-3-ol as the main components of the male-produced aggregation pheromone of *H. halys*. Both attracted females, males and nymphs in the field. Mixtures of eight stereoisomers containing these two components were also attractive, indicating that additional stereoisomers did not hinder attraction, and the authors noted that relatively inexpensive mixtures could therefore be used.

Leskey et al. (2015) extended this with the compound (10,11-epoxy-1-bisabolen-3-ol) that can exist as 16 stereoisomers, of which the natural pheromone is a 3.5:1 mixture of (3*S*,6*S*,7*R*,10*S*) and (3*R*,6*S*,7*R*,10*S*). Some treatments containing none of the natural components were moderately active in the field, indicating that certain stereoisomers resemble the pheromone closely enough to trigger a response. Mixtures containing the pheromone components remained highly attractive in the presence of multiple unnatural stereoisomers, and captures were dose-dependent for pheromonal and non-pheromonal lures alike. Unnatural stereoisomers of the *H. halys* pheromone therefore did more than fail to interfere: some attracted bugs on their own, and none reduced attraction to the natural components.

Halyomorpha halys is also attracted to methyl (2*E*,4*E*,6*Z*)-decatrienoate (MDT), the pheromone of *Plautia stali*, a stink bug that is sympatric with *H. halys* in Asia. MDT also synergises attraction to the *H. halys* pheromone. Weber et al. (2020) found that captures were relatively insensitive to the ratio of pheromone to MDT, provided both were present. Captures tracked the loading of the major (3*S*,6*S*,7*R*,10*S*) stereoisomer but were relatively insensitive to

the minor (3*R*,6*S*,7*R*,10*S*) stereoisomer. The receiver therefore largely ignores a stereoisomer that the producer makes, a point we return to under Biosynthetic Origin of Stereochemistry. In collaborative trials in the United States and Europe, pheromone loading affected captures more than MDT loading, and lower pheromone loading could be offset by more MDT, which is cheaper to produce (Leskey et al. 2021).

The harlequin bug, *Murgantia histrionica*, uses two stereoisomers of the same compound, (3*S*,6*S*,7*R*,10*S*)- and (3*S*,6*S*,7*R*,10*R*)-10,11-epoxy-1-bisabolen-3-ol, produced in a 1.4:1 ratio (Khrimian et al. 2014a). The two species thus share a carbon skeleton and ring configuration but differ in which stereocentre varies within the natural blend: C3 in *H. halys* and C10 in *M. histrionica*.

Not every stink bug system has been resolved stereochemically. Males of the sloe bug, *Dolycoris baccarum*, produce α -bisabolol, *trans*- α -bergamotene and β -bisabolene in a ratio of 100:10:3 (Yang et al. 2019). In the field, ($\pm$)- α -bisabolol alone attracted adults, and its activity was synergised by *trans*- α -bergamotene but not by (*S*)- β -bisabolene. A 10:1 blend of the two active compounds was less attractive than caged live males, and the authors concluded that the absolute configuration of the natural components remains undetermined. Whether the shortfall reflects stereochemistry or missing components remains unclear.

Beyond Heteroptera. The ambrosia beetle *G. sulcatus* produces its aggregation pheromone, sulcatol, as a 65:35 mixture of (*S*)-(+)- and (*R*)-(-)-enantiomers, determined by NMR of Mosher ester derivatives of material from boring dust (Byrne et al. 1974). In laboratory and field bioassays, the beetles responded only when both enantiomers were present; neither enantiomer alone was more attractive than solvent controls (Borden et al. 1976). This was the first demonstration that the enantiomers of an attractive pheromone can act synergistically. Borden et

al. (1976) also reported a greater response to racemic sulcatol than to the natural 65:35 ratio, but the same group later attributed that result to experimental artefact (Borden et al. 1980). Their more extensive tests showed synergism at every ratio containing at least 10% of either enantiomer in the laboratory, a field response when as little as 1 or 2% of (*R*) was present, and no differences among stimuli containing at least 25% of either enantiomer. *G. sulcatus* is therefore the clearest documented case of a broad ratio plateau. Its congener *G. retusus*, as described above, is at the opposite extreme.

Ips pini spans both extremes within a single species. Idaho and California populations produce (–)-ipsdienol and are inhibited by (+) (Birch et al. 1980; Lanier et al. 1980). New York beetles produce (+)- and (–)-ipsdienol in a 65:35 ratio, respond much more strongly to (+) than to (–), and in the field responded best to a 50:50 mixture (Lanier et al. 1980). Reciprocal hybrids between New York and Idaho beetles resembled New York beetles, and the genes controlling the difference were not sex-linked. In Wisconsin and Michigan, blends of 75:25 or 50:50 (+):(–) caught the most *I. pini* in both years at both sites, and a 25:75 blend also caught more than controls (Herms et al. 1991). The clerid predator *Thanasimus dubius*, which uses ipsdienol as a kairomone, was attracted to all blends tested, and prey and predator preferences varied between sites and years. Herms et al. (1991) noted that this lability has consequences for mass trapping with a single blend.

In the bean beetle, *Acanthoscelides obtectus*, males produce methyl (*E,R*)-2,4,5-tetradecatrienoate with a smaller amount of the (*S*)-enantiomer, at about 9:1 (Mohan-Kumar et al. 2025). The pure (*R*)-enantiomer was active in electroantennography alone, in the 9:1 blend and in the racemate, whereas the pure (*S*)-enantiomer was inactive. In an olfactometer, females responded only to (*R*), and the pure (*R*)-enantiomer was as active as the 9:1 blend. Adding (*S*) at

up to 10% had no effect, but adding it in equal proportion, with the amount of (*R*) held constant, enhanced female preference. The authors did not determine the proportion at which (*S*) shifts from inactive to synergistic, and they have not yet tested the result in the field. They proposed racemic material as the basis for surveillance.

The boll weevil, *Anthonomus grandis*, illustrates inertness rather than tolerance (Dickens and Mori 1989). The electroantennogram threshold for (+)-grandisol was 100 to 1000 times lower than for its antipode, and (–)-grandisol elicited single-cell responses only at very high doses. In the field, (+)-grandisol combined with the three other pheromone components was significantly more attractive than the same blend with (–)-grandisol, whose low activity could be attributed to the other components alone. Adding (–)- to (+)-grandisol at equal dosage produced only slight, non-significant inhibition. The antipode is therefore barely perceived and behaviourally neutral. These conclusions rest on single-sensillum recordings from only two neurons tested with the pure enantiomers, and the authors cautioned that (–)-grandisol-specific cells could not yet be excluded.

Moth congeners of strict species show that an antipode can be either inert or tolerated. The nun moth, *L. monacha* (reported as *Porthetria monacha*), responded to increasing concentrations of (+)-disparlure regardless of the addition of (–)-disparlure, which drastically suppresses the spongy moth (Klimetzek et al. 1976). Single-sensillum recordings later showed that in the spongy moth neighbouring receptor cells respond to (+)- and (–)-disparlure respectively, whereas in the nun moth both cells respond to (+)-disparlure, and electroantennograms show no sensitivity to (–)-disparlure (Hansen 1984). The antipode is therefore inert for the nun moth rather than tolerated. Among winter-flying geometrids, *A. marginaria* was attracted to (3*Z*,9*Z*)-(6*S*,7*R*)-epoxynonadecadiene, and adding the (6*R*,7*S*)-enantiomer did not affect its captures,

whereas it reduced captures of *Erannis defoliaria*, which uses the same (6*S*,7*R*)-epoxide as its pheromone (Szöcs et al. 1993). The pheromone produced by *A. marginaria* females has not been identified, so this is tolerance of an attractant rather than of the natural pheromone. Between these extremes, *Colotois pennaria* and *E. defoliaria* each use one enantiomer of the same epoxide; each pure enantiomer attracted only conspecific males, and the racemate caught significantly fewer males of both species than the corresponding pure enantiomer (Szöcs et al. 1993).

Tolerance can also depend on the amount of antipode present. The southern pine engraver, *I. calligraphus*, responded to its two-component pheromone of ipsdienol and cis-verbenol only when the (*S*)-enantiomer of cis-verbenol was present. (*R*)-cis-Verbenol did not significantly alter the response when released in amounts comparable to (*S*), but it drastically suppressed the response at a tenfold or greater excess (Vité et al. 1976).

At the far end of the spectrum, the natural stereoisomer can be the least active one. Females of the German cockroach, *Blattella germanica*, produce (3*S*,11*S*)-3,11-dimethylnonacosan-2-one as a contact sex pheromone. At high doses all four stereoisomers elicited courtship from every male tested, but at physiologically relevant doses the natural isomer was the least effective (Eliyahu et al. 2004). This is the first reported case of a natural stereoisomer being less active than stereoisomers that do not occur naturally. A related hydrocarbon, 3,11-dimethylnonacosane, has recently been synthesised as all four stereoisomers; all triggered aggregation in Y-tube, semi-field and electroantennogram assays, with the (3*S*,11*S*)-isomer most active (Zhou et al. 2026). The odorant-binding proteins OBP39 and OBP40 bound (3*S*,11*S*)-3,11-dimethylnonacosane, and silencing either abolished antennal responses and reduced aggregation. Because the configuration produced by the cockroach is not known, and the compound had not previously

been validated as a pheromone component, this result cannot yet be read as tolerance of unnatural stereoisomers.

Cues Rather than Signals. Kairomones differ from pheromones in that the emitter is not selected to communicate, so receiver responses to their stereoisomers are not shaped by signal–receiver coevolution. They nevertheless show the same range of responses. In *Aedes aegypti* and *Culex quinquefasciatus*, a maxillary palp olfactory neuron responded more strongly to (*R*)- than to (*S*)-1-octen-3-ol at doses from 10^{-9} to 10^{-6} g in both species (Cook et al. 2011). Behaviourally, *Ae. aegypti* showed increased attraction only to the (*R*)-enantiomer, and an 84:16 (*R*:*S*) mixture, based on the ratio in cattle breath, had no positive effect. In *Cx. quinquefasciatus*, the 84:16 mixture reduced non-sustained flight at seven of the doses tested, suggesting an excitatory effect, whereas at the highest dose the treatments containing (*R*) reduced relative attraction and the (*S*)-enantiomer did not. The two species thus differ in behavioural response to the same enantiomers, and in *Culex* the sign of the response depends on dose. In *Anopheles gambiae*, the labellum-expressed receptor AgamOr29 was activated by (*R*)-linalool and, with a lower EC_{50} , by a linalool mixture of undetermined enantiomeric composition (Huff and Pitts 2019). Pure (*S*)-linalool was not tested, and the authors inferred that (*S*) is probably the more effective ligand.

IS IT REAL? METHODOLOGICAL CAUTIONS

Any apparent tolerance of an unnatural stereoisomer must first be distinguished from contamination. No synthetic chiral compound is perfectly pure: japonilure had not been obtained above 99% optical purity when Leal (1996) noted that an antennal response to such a sample may come from receptors tuned to the minor antipode, and he therefore used chiral GC-electroantennographic detection to deliver each enantiomer free of its antipode. Szöcs et al. (1993) worked with epoxides of about 95% ee, with detection limits for the minor enantiomer of

0.5 to 1% in synthetic samples and 2 to 3% in gland extracts, and they cautioned that responses attributed to the unnatural enantiomer might have been evoked by trace natural enantiomer. Traces matter because receivers can be exquisitely sensitive to them: 5% of the antipode abolished response in *A. osakana* (Leal 1996) and virtually eliminated it in Californian *I. pini* (Birch et al. 1980), and *G. sulcatus* responded when 1 to 2% of (*R*)-sulcatol was present (Borden et al. 1980). Borden et al. (1980) themselves concluded that their results showed the fallibility of experiments using pheromones of less than 100% optical purity.

Early reports of antipode activity have been overturned on exactly these grounds. Mori et al. (1978) reported that synthetic (–)-grandisol of 91 to 98% optical purity was as active as the isolated natural pheromone component in laboratory assays with female boll weevils. Dickens and Mori (1989) attributed that result to enantiomers that were not optically pure and to reliance on a few no-choice laboratory assays. Vité et al. (1976) warned that racemates used to mimic pheromones produced naturally as single enantiomers can give misleading results, because an inhibitory antipode may act only above a threshold concentration. Their observation that inhibition required a higher saturation of receptor sites than attraction led them to suggest that this explains why low concentrations of optically impure synthetics often mimic pheromones successfully.

The natural composition must also be measured reliably. Plummer et al. (1976) described two methods then available, Mosher ester derivatives and chiral lanthanide shift reagents, applied to 50 to 500 µg of natural material. Values reported as 100% therefore mean optically pure within detection limits. Receptor-level data carry their own caveat: the enantioselectivity of the *I. typographus* receptor ItypOR46 was lower when it was expressed in *Xenopus* oocytes than in

HEK cells (Yuvaraj et al. 2021), so selectivity measured in a single heterologous system should be treated as provisional.

We suggest that a case should be classed as chiral flexibility only when (i) the natural stereoisomeric composition has been determined with a stated detection limit; (ii) the non-natural stereoisomer has been tested at graded proportions, including excess, and not only as a racemate; (iii) the purity of the synthetic material is reported; and (iv) behaviour has been measured in the field or in a choice assay. Electrophysiology is additionally needed to distinguish tolerance from inertness. Few of the cases in Table 1 meet all four criteria and meeting them should be a priority.

MECHANISMS

Receptor Architecture. The existence of receptors tuned to each enantiomer within a single antenna was first suggested for scarabs by chiral GC-electroantennographic detection: antennae of both *A. osakana* and *P. japonica* responded to both enantiomers of japonilure, more strongly to the enantiomer produced by conspecific females (Leal 1996). Earlier single-sensillum recording work had found scarab pheromone receptors responsive only to the natural enantiomer, and Leal argued that the electroantennogram response to the antipode indicated separate receptors. Thirty years later, Wang et al. (2026) identified these receptors. Single sensillum recordings in *A. corpulenta* revealed two sensillum types, one narrowly tuned to (*R*)-japonilure and one responding to both enantiomers, with lower sensitivity to (*S*). In two-electrode voltage clamp recordings, AcorOR18 was selective for (*R*)-japonilure, whereas AcorOR29 was activated by both enantiomers, and the two receptors appear to be expressed in different sensillum types. RNA interference knockdown of either receptor reduced male attraction to (*R*)-japonilure, and knockdown of both abolished it. The broadly tuned receptor therefore contributes to attraction,

not only to antagonism. Of three orthologous receptors in *P. japonica*, PjapOR42 and PjapOR37 were strictly selective for (*R*)-japonilure, whereas PjapOR39 responded to both enantiomers and more strongly to the antagonist (*S*). The authors suggested that PjapOR39 may mediate the antagonism. The *P. japonica* data come only from oocyte recordings, which carries the caveat noted under Methodological Cautions.

These results suggest that strict and flexible responses need not reflect different receptor repertoires. Both can arise from narrowly and broadly tuned receptors weighted differently. Several lines of evidence indicate that the weighting occurs centrally. In *Ips*, single-sensillum recordings found two receptor cell types, each specialised to one enantiomer of ipsdienol, with no synergistic or inhibitory interaction between enantiomers at the level of the receptor cell (Mustaparta et al. 1980). *Ips paraconfusus* had most of its ipsdienol cells keyed to (+) and western *I. pini* most keyed to (–), consistent with the species' behaviour. Eastern *I. pini*, however, also had more (–) than (+) cells, even though this population produces mostly (+)-ipsdienol and requires both enantiomers; the cell counts were small (nine to eleven cells per group) and the eastern difference was not statistically robust. Because the receptor systems of the two *I. pini* populations appeared similar while their behaviour differed, Lanier et al. (1980) concluded that the difference is governed centrally. Behavioural interruption by the opposite enantiomer, without inhibition at the receptor neuron, points the same way (Birch et al. 1980).

The strongest evidence comes from the geometrids. Szöcs et al. (1993) measured electroantennogram dose–response slopes for the natural and unnatural enantiomers in three species (five antennae each). The slope ratio was about 3.2 in *C. pennaria* (25.26 vs 7.86), 2.4 in *E. defoliaria* (30.36 vs 12.74), and 5.1 in *A. marginaria* (21.21 vs 4.15). The species whose behaviour tolerates the antipode therefore showed the sharpest peripheral discrimination of the

three. Peripheral discrimination and behavioural fidelity can evidently be decoupled, and behavioural valence may depend on which channels are recruited and how they are weighted rather than on how cleanly the antenna resolves the enantiomers.

Receptor studies from other systems suggest how broad tuning could arise. In the spruce bark beetle, *I. typographus*, ItypOR46 responds to (*S*)-ipsenol and ItypOR49 to (*R*)-ipsdienol; responses to the antipodes were attributed to trace impurity (Yuvaraj et al. 2021). Homology modelling and docking predicted a binding cleft in ItypOR46 in which the ligands interact with Tyr84 and Thr205, and site-directed mutagenesis supported the importance of these residues, with hydrogen bonding appearing key to binding. In *Spodoptera*, the pheromone receptor SlitOR5 of *S. littoralis* is narrowly tuned to (*Z,E*)-9,11-tetradecadienyl acetate, whereas its orthologues in *S. exigua* and *S. frugiperda* are broadly tuned to several pheromone compounds (Li et al. 2023). Ancestral gene resurrection showed that narrow tuning evolved in only one of two copies produced by a duplication, through changes at eight binding-pocket positions. These ligands are geometric and positional isomers rather than enantiomers, but the result shows that broad tuning can be ancestral and narrow tuning derived. It is therefore our interpretation, rather than a finding of that study, that relaxed stereochemical fidelity need not represent degradation of a once-strict system. The cryo-transmission electron microscopy structure of MhOR5 from the jumping bristletail *Machilis hrabei*, a homotetrameric odorant-gated ion channel, showed that eugenol and DEET are recognised through distributed hydrophobic interactions within the same geometrically simple pocket, and mutating single pocket residues reconfigured the receptor's tuning (del Mármol et al. 2021). The authors noted that such a pocket relaxes orientational constraints on ligands. MhOR5 is not a pheromone receptor and its ligands are achiral, but a pocket of this kind offers a plausible structural basis for accepting both enantiomers of a ligand.

Structures of odorant receptor–Orco complexes from two mosquitoes and the pea aphid have since shown that a single tuning receptor subunit assembles with three Orco subunits, and that activation of this one subunit can open the channel (Wang et al. 2024; Zhao et al. 2024). Mapping experimentally identified functional residues from receptors of several insect orders, including *I. typographus*, onto the structure of the pea aphid receptor ApisOR5 revealed recurring hotspots within the binding pocket (Li et al. 2026). Structures of a receptor bound to each enantiomer of a chiral pheromone would show directly how one pocket accepts or rejects mirror-image ligands.

Dose. Several of the cases above show that the effect of an unnatural stereoisomer depends on its amount. In *I. calligraphus*, (*R*)-cis-verbenol was neutral at amounts comparable to the pheromone but suppressive at a tenfold excess (Vité et al. 1976). In the gypsy moth, a small proportion of (–)-disparlure was less repressive than the racemate, and a higher proportion drastically reduced the response. Vité et al. (1976) concluded that inhibition by the unnatural enantiomer requires greater receptor-site saturation than attraction by the pheromone. In *G. sulcatus*, stimuli containing more than 97% (*R*)-sulcatol elicited no response, which Borden et al. (1980) interpreted as inhibition by high concentrations of (*R*). In *Cx. quinquefasciatus*, treatments containing (*R*)-1-octen-3-ol reduced relative attraction only at the highest dose (Cook et al. 2011).

At the antenna, discrimination between enantiomers improves with dose. In all three geometrids examined by Szöcs et al. (1993), electroantennogram responses to the two enantiomers were similar at low doses and diverged at higher doses, because the natural enantiomer had the steeper dose–response slope. This runs against the intuition that higher doses should blur discrimination by recruiting more receptors.

Studies with achiral odorants show how behavioural valence can change with concentration. In adult *Drosophila melanogaster*, apple cider vinegar is attractive at low concentration through the activation of two glomeruli, DM1 and VA2, whereas a higher concentration excites an additional glomerulus whose activation results in reduced attraction (Simmelhack and Wang 2009). *Drosophila* larvae show the reverse pattern for (*E*)-2-hexenal, which is aversive at low concentration and attractive at higher concentration (Perry et al. 2024). At low concentration, activation of the neuron expressing Or7a alone drives avoidance, and at higher concentrations additional attraction-conveying neurons, those activated by odorants known to activate Or42a and Or85c, override it. In both cases, valence changes because different receptor channels are recruited, not because any single receptor changes. In the seven-spot ladybird, *Coccinella septempunctata*, butyl salicylate attracted females at 10 µg and repelled them at 100 µg, with corresponding effects on predation (Liang et al. 2026). The receptor CsepOR1, the most highly expressed of 24 odorant receptors in the antennae, was narrowly tuned to butyl salicylate among 362 odorants tested. Whether additional receptors are recruited at the higher dose was not tested, so this case may or may not fit the recruitment model. None of these studies used chiral compounds, and whether enantiomeric discrimination by a receiver changes with dose in the same way remains to be tested directly.

Biosynthetic Origin of Stereochemistry. The possibility that biosynthesis limits stereochemical precision was raised when the first pheromone enantiomeric ratio was measured. Byrne et al. (1974), finding that *G. sulcatus* produces sulcatol as a 65:35 mixture of enantiomers, noted that if the beetle makes all of it, the situation appears wasteful, requiring either an enzyme of low specificity or a useless enzyme, unless both enantiomers are perceived. Naturally produced enantiomeric mixtures are not unusual. Plummer et al. (1976) reported *trans*-verbenol

from the southern pine beetle, *Dendroctonus frontalis*, as a 60:40 (+):(-) mixture and seudenol from the Douglas-fir beetle, *D. pseudotsugae*, as a racemic (50:50) mixture, alongside sulcatol at 65:35 (+):(-). Eastern *I. pini* produces (+)- and (-)-ipsdienol at 65:35 (Lanier et al. 1980), *A. obtectus* produces its pheromone at about 9:1 (*R*):(*S*) (Mohan-Kumar et al. 2025), and *M. histrionica* and *H. halys* each produce two stereoisomers (Khrimian et al. 2014a, 2014b). The only explicit biosynthetic explanation in Mori (2007) is for the German cockroach, whose natural pheromone stereoisomer is the least active of four: Mori attributed this to stereochemical restriction during biosynthesis.

The enzymes responsible for insect terpenoid pheromones are now being identified, which makes the question testable. Insect terpene synthases evolved independently of those of plants, fungi and bacteria, from *trans*-isoprenyl diphosphate synthases (IDSs). In the flea beetle *Phyllotreta striolata*, whose male-produced aggregation pheromone includes (6*R*,7*S*)-himachala-9,11-diene, crude protein extracts showed terpene synthase activity only with (*Z,E*)-farnesyl diphosphate [(*Z,E*)-FPP] as substrate (Beran et al. 2016). No sequences resembling plant, fungal or bacterial terpene synthases were found in the transcriptome, but nine divergent *trans*-IDS-like transcripts were identified, four of whose products had terpene synthase activity. Recombinant PsTPS1 converted (*Z,E*)-FPP to a mixture of sesquiterpenes including the pheromone, and RNA interference knockdown reduced pheromone emission. The same enzyme converted (*Z,Z*)-FPP to (*R*)- β -bisabolene, so its stereochemical output depends on its substrate. Conserved exon-intron structures indicated descent from *trans*-IDS ancestors. In male *I. pini*, a geranyl diphosphate synthase regulated by juvenile hormone III is expressed almost exclusively in the anterior midgut, the site of pheromone biosynthesis, establishing *de novo* synthesis of monoterpene pheromone components rather than modification of dietary precursors (Gilg et al. 2005). Because

geranyl diphosphate is achiral, the configuration of ipsdienol is set further downstream. The myrcene hydroxylases CYP9T1 and CYP9T2, from *I. confusus* and western *I. pini*, produce ipsdienol of intermediate enantiomeric composition, about 80:20 (-):(+) , whereas western *I. pini* responds to a blend of about 97:3, implying a further adjustment of the ratio (Figueroa-Teran et al. 2012 and references therein). Figueroa-Teran et al. (2012) identified an ipsdienol dehydrogenase (IDOLDH), expressed mainly in the anterior midgut of fed males, that oxidised racemic and (4*R*)-ipsdienol to ipsdienone but did not use (4*S*)-ipsdienol as a substrate. They proposed that this enzyme, together with stereospecific reduction of ipsdienone, tunes the enantiomeric ratio of ipsdienol. In *Ips*, as in the stink bugs discussed below, the stereochemistry of the final pheromone therefore appears to be set by enzymes acting after the carbon skeleton has been formed.

In stink bugs, the stereospecific step is known, and it is not where the natural stereoisomeric blend is determined. The harlequin bug enzyme MhTPS converts (*E,E*)-FPP stereospecifically to (1*S*,6*S*,7*R*)-sesquipiperitol, whose C6 and C7 configurations match those of the pheromone (Lancaster et al. 2018). MhTPS is expressed in the tissue lining the abdominal sternites of mature males, and RNA interference confirmed its role in pheromone production. It derives from a *trans*-IDS progenitor, and structure-guided mutagenesis identified residues critical to its activity. Sesquipiperitol also occurs in plants, indicating convergent evolution. In the southern green stink bug, *Nezara viridula*, the FPP synthase NvFPPS produces (*E,E*)-FPP, and the IDS-type terpene synthase NvTPS converts it to (+)-(*S,Z*)- α -bisabolene (Lancaster et al. 2019). This is the presumed precursor of the sex pheromone, a 3:1 mixture of *trans*- and *cis*-(*Z*)- α -bisabolene epoxides in the population studied. The epoxidation is thought to be catalysed by a cytochrome P450 that has not yet been identified. The *H. halys* enzyme HhTPS1 produces sesquipiperitol

with the same (1*S*,6*S*,7*R*) configuration as MhTPS (Rebholz et al. 2023). IDS-type terpene synthases arose at the onset of pentatomid evolution more than 100 million years ago, coinciding with the rise of flowering plants, and have since diversified little, in contrast to plant terpene synthases. A similar evolution occurred independently in beetles.

Taken together, these results locate the variable stereocentres downstream of the terpene synthase. In each species, the terpene synthase makes a single stereoisomer, yet the natural pheromone contains two: differing at C10, the epoxidised carbon, in *M. histrionica*; differing at C3 in *H. halys*; and a *trans/cis* epoxide pair in *N. viridula*. Because HhTPS1 makes a single stereoisomer, at least one of the two *H. halys* components must acquire its configuration in a later step. Rebholz et al. (2023) reached a compatible conclusion: a few conserved terpene synthase genes, together with a small number of subsequent isomerisation and epoxidation steps, generate species-specific isomeric blends. None of those later enzymes has yet been characterised. The observation that *H. halys* captures are largely insensitive to the minor stereoisomer (Weber et al. 2020) suggests a case in which biosynthetic imprecision at a downstream step is matched by receiver indifference at the same stereocentre.

Termites show that the enantiomeric composition of the product from a terpene synthase can itself evolve readily. A family of terpene synthases arose by duplication of geranylgeranyl diphosphate synthase in the ancestor of the Neoisoptera, with transposable elements enriched at these loci (Horáček et al. 2026). Within this family, EneoC from *Embiratermes neotenicus* produces pure (3*R*,6*E*)-nerolidol, the queen pheromone, whereas EneoE produces racemic (6*E*)-nerolidol, and NtGGPPS6 from *Nasutitermes takasagoensis* produces 65% of the (*R*)-enantiomer. A single substitution in NtGGPPS6, T152I, raised this to 91% (*R*), close to the selectivity of EneoC, and also abolished its ability to cyclise geranylgeranyl diphosphate to

neocembrene. The enantiomeric ratio a species produces is therefore an evolvable trait that single mutations can shift. EneoC produces the queen pheromone *in vivo*, as shown by RNA interference; it is strongly upregulated in queens, ranks among the most abundant queen proteins, and is expressed only in the queen epidermis, within mitochondria-derived structures in class 1 secretory cells (Štáfková et al. 2026). EneoC and the FPP synthase EneoB both carry mitochondrial targeting sequences, suggesting that they are colocalised, and eggs acquire the pheromone from queens rather than synthesising it.

Terpene synthases have also originated independently in Lepidoptera. In *Heliconius melpomene*, HmelOS synthesises the anti-aphrodisiac (*E*)- β -ocimene *in vitro*, whereas its orthologue in *H. cydno*, which lacks the compound, showed no activity, indicating a coding rather than regulatory difference (Darragh et al. 2021). These enzymes group with geranyl and geranylgeranyl diphosphate synthases rather than with the terpene synthases of Hemiptera and Coleoptera. (*E*)- β -Ocimene is not chiral, so this case bears on the independent origin of insect terpene synthases rather than on stereochemistry. Terpene synthases and pathways across animals have been reviewed by Tholl et al. (2023), who proposed that modification of substrate-binding motifs in canonical IDS proteins facilitated the transition to terpene synthase function early in insect evolution.

ECOLOGICAL AND EVOLUTIONARY EXPLANATIONS

Community Context. Borden et al. (1976) suggested that synergistic or enantiomer-specific responses could provide reproductive isolation between species that use different enantiomers or enantiomeric ratios of the same compound. Borden et al. (1980) tested this with sympatric *Gnathotrichus* species: *G. retusus* produces and responds to (*S*)-sulcatol and is inhibited by (*R*), whereas *G. sulcatus* requires both. In the field, each species was trapped preferentially by its own

stimulus, and the authors noted that the two species rarely inhabit the same host. In California, *I. pini* and *I. paraconfusus* each produce an enantiomer of ipsdienol that interrupts the other's response, a system of mutual interruption that prevents even chance encounters (Birch et al. 1980).

The geometrids offer the most direct comparison. *C. pennaria* and *E. defoliaria* use opposite enantiomers of the same epoxide, share habitats, have partially overlapping flight periods and coincide in their diurnal rhythm of calling and mating (Szöcs et al. 1993). For *E. defoliaria*, the (6*R*,7*S*)-enantiomer used by *C. pennaria* reduced captures, whereas for the late winter/early spring-flying *A. marginaria*, which is attracted to the same (6*S*,7*R*)-epoxide as *E. defoliaria*, it did not. Szöcs et al. (1993) suggested that this difference reflects species specificity in the communication channel: *C. pennaria* flies at the same time as *E. defoliaria*, whereas no species using the (6*R*,7*S*)-enantiomer was found during the flight period of *A. marginaria*. In this view, fidelity is tight when a synchronous species uses the antipode and relaxed when none does. The same study, however, contains a case the hypothesis does not explain: *A. aurantiaria* is strongly antagonised by its antipode, even though no species using (3*R*,4*S*)-epoxynonadecadiene during its flight period was identified. The community-context hypothesis is therefore supported by one comparison within this group but not by the other, and it predicts, rather than yet demonstrates, a general pattern. Stereochemistry is also not the only isolating mechanism in these systems: *A. osakana* flies mainly in the hour after sunset whereas *P. japonica* is active mainly in daylight (Leal 1996).

This view places chiral signals within the broader literature on the evolution of pheromone channels. Sex pheromones have traditionally been viewed as species-recognition signals under stabilising selection, but variation in signals and responses within and between populations is

now recognised as a possible driver of divergence, through its effects on mate choice and gene flow (De Pasqual et al. 2021). Female signals and male preferences can change together, but identifying the genes underlying such variation remains difficult (Groot et al. 2016). In noctuid moths, direct evidence linking molecular changes in biosynthesis and reception to lineage divergence remains limited (Cao et al. 2026). Across 99 drosophilid species, pheromones and their olfactory channels evolve rapidly and independently (Khallaf et al. 2021), and in the leaf beetle *Galerucella grisea*, divergence in female cuticular wax between flight-capable and flightless populations is accompanied by divergent male preference (Chiba et al. 2025). None of these studies addresses stereochemistry directly, although De Pasqual et al. (2021) cite a mutation in an enzyme that changes the stereochemistry of a pheromone component as an example of a saltational evolutionary change, the kind of change that Horáček et al. (2026) produced experimentally with a single amino acid substitution. The chiral systems reviewed here offer an unusually clean test, because the signal difference is confined to configuration.

Signal Complexity. Leal (1996) proposed that the partial tolerance shown by *C. pennaria* and *E. defoliaria* arises because, in these species, the chiral compound is only one component of a multicomponent pheromone, so an antagonistic effect of the antipode might be better tolerated than in a single-component system. On this hypothesis, species with single-component pheromones must carry all their specificity in stereochemistry and cannot tolerate the antipode.

Existing data partially support this hypothesis. Single-component systems include the strictest cases: *A. osakana* (Leal 1996) and *G. retusus*, for which fractionation gave no evidence of more than one attractive compound (Borden et al. 1980). Multicomponent systems include tolerant or inert cases: the boll weevil, whose four-component pheromone was not significantly inhibited by the antipode of grandisol (Dickens and Mori 1989), and *H. halys*, whose response is

synergised by MDT and is largely insensitive to the minor stereoisomer (Weber et al. 2020). The geometrids, whose epoxides act with hydrocarbons that are not attractive alone but enhance captures (Szöcs et al. 1993), show reduced but not abolished responses to the racemate. There are exceptions. *G. sulcatus* uses a single compound yet tolerates a wide range of enantiomeric ratios (Borden et al. 1980), and *I. calligraphus* uses a two-component pheromone yet is suppressed by an excess of (*R*)-*cis*-verbenol (Vité et al. 1976). A formal test would require a comparative analysis that controls for phylogeny and sympatry.

APPLIED CONSEQUENCES

How receivers respond to stereoisomers matters economically because stereoselective synthesis often dominates the cost of chiral lures. Where fidelity is relaxed, mixtures of stereoisomers can replace the enantiopure compound. This is already practice for *H. halys*, for which mixtures containing the pheromone components and non-natural stereoisomers remain attractive (Khrimian et al. 2014b; Leskey et al. 2015), captures are insensitive to the minor stereoisomer (Weber et al. 2020), and pheromone loading can be traded against the cheaper synergist (Leskey et al. 2021). Borden et al. (1980) concluded that racemic sulcatol could be used with confidence against *G. sulcatus*, for which a pheromone-based suppression programme was already operating in a commercial sawmill, and Mohan-Kumar et al. (2025) proposed racemic material for bean beetle surveillance. Mori (2007) made the general point that pheromones whose antipodes are non-inhibitory can be deployed as racemates.

The cost of enantiopure material, however, depends less on chirality as such and more on whether a cheap natural source can supply the insect's configuration. Leptotriene, a sesquiterpene produced by males of the leaf-footed bugs *Leptoglossus zonatus* and *L. occidentalis*, has the same (1*S*,8*R*) configuration as plant-derived (–)-(*E*)-β-caryophyllene, from which it can be

557 synthesised cheaply (Millar et al. 2022). While leptotriene elicits responses in both sexes, its role
558 as a pheromone remains unconfirmed in the field. By contrast, Aldrich et al. (1993) found that
559 males of the banana-spotting bug, *Amblypelta lutescens lutescens*, release male-specific
560 monoterpenes and sesquiterpenes, apparently from cells in the cuticular epidermis rather than
561 from the metathoracic scent glands, which are not sexually dimorphic in this species. The major
562 component in *A. l. lutescens* and in the Nearctic coreid *L. phyllopus* is (3*R*)-(E)-nerolidol,
563 whereas plants commonly produce (3*S*)-(E)-nerolidol. Natural sources of the (*R*)-enantiomer are
564 few. About 90% of the fruit essential oil of the Cameroonian *Aframomum pruinsum* is (E)-
565 nerolidol, identified as the (*R*)-enantiomer from the optical rotation of the oil (Menut et al. 1994),
566 and the seed essential oils of *A. pruinsum* and two congeners contain more than 88% (3*R*)-(E)-
567 nerolidol (Nguikwie et al. 2013). The termite *Embiratermes neotenicus* also produces (3*R*,6*E*)-
568 nerolidol as a queen pheromone (Horáček et al. 2026; Štáfková et al. 2026). None of these has
569 been developed as a commercial source, and the (*R*)-enantiomer is instead synthesised, for
570 example in three steps from (E,E)-farnesol via Sharpless asymmetric epoxidation (Le and
571 Chauhan 2014). Khrimian et al. (2012) identified a further male-specific component of *A. l.*
572 *lutescens*, (R,E,E)- α -farnesene-10,11-oxide, and confirmed that males produce a single
573 enantiomer of each chiral component. They synthesised (3*R*)-(E)-nerolidol by a four-step route
574 using Sharpless asymmetric epoxidation (93% ee) and the epoxide by asymmetric
575 dihydroxylation of a sulfolene (95% ee), and showed that a blend of (E,E)- α -farnesene, (3*R*)-(E)-
576 nerolidol and the epoxide attracted males, females and nymphs in a mango orchard. New
577 sesquiterpenes continue to be described from coreids, and each raises the same question: is the
578 enantiopure compound needed, or would a mixture serve? We therefore predict that relaxed

fidelity will be most valuable in systems whose configuration is opposite to that commonly available from plants.

For practical use, we suggest that the substitution of a mixture for an enantiopure compound should be justified by the evidence standard proposed under Methodological Cautions, together with two applied checks. The first is whether a sympatric species uses the antipode, since a racemic lure could then fail through inhibition, as in *I. pini* and *G. retusus*, or attract non-target species. The second is whether the response is stable across sites and years, which Herms et al. (1991) found it was not for *I. pini* and its predator.

OUTSTANDING QUESTIONS AND A COMPARATIVE AGENDA

The central gap is that the three classes of explanation have never been tested against one another within a single clade. Doing so requires, for a set of related species, the natural stereoisomeric composition, the receiver's behavioural response to graded stereoisomer proportions, receptor-level data distinguishing inert from tolerated stereoisomers, the stereoselectivity of the relevant biosynthetic enzymes, and the presence of synchronously active species using the antipode. Each hypothesis makes a distinct prediction. Receptor weighting predicts that fidelity varies with the relative representation or central weighting of broadly tuned receptors, independent of periphery-level discrimination, as the geometrid data suggest. Biosynthetic constraint predicts that receivers tolerate variation at stereocentres that the producer sets imprecisely, and not at stereocentres it sets precisely. Community context predicts that fidelity is tightest where a synchronous species uses the antipode.

Two groups are already close to supporting such a test. In *Ips*, strict and flexible populations and species occur together, single-sensillum recording data on enantiomer-specific receptor cells exist (Mustaparta et al. 1980), enantiomer-selective odorant receptors have been characterised

(Yuvaraj et al. 2021), the early steps of pheromone biosynthesis are known (Gilg et al. 2005), and candidate enzymes that set the enantiomeric composition of ipsdienol have been identified (Figueroa-Teran et al. 2012). What is missing is a comparison of these enzymes, and of receptor representation, between strict and flexible populations. In Pentatomidae, the stereospecific terpene synthases of three species are characterised (Lancaster et al. 2018, 2019; Rebholz et al. 2023), stereoisomer libraries exist for the bisabolane pheromones (Khrimian et al. 2014a, 2014b), and receiver tolerance has been measured for *H. halys* (Leskey et al. 2015; Weber et al. 2020). The enzymes that set the variable stereocentres downstream of the terpene synthase are the obvious next target. A specific prediction is that receiver tolerance should be greatest at those stereocentres. In the geometrids, identifying the pheromone of *A. marginaria* and searching for species that use (3*R*,4*S*)-epoxynonadecadiene during the flight period of *A. aurantiaria* would test the community-context hypothesis directly.

CONCLUSIONS

The ways in which insects respond to non-natural stereoisomers have been well catalogued, and the most common response, indifference to the antipode, has long been exploited in practice. What has been missing is an explanation of why species differ. The evidence reviewed here indicates that the answer lies in at least three places: how narrowly and broadly tuned receptors are weighted centrally; which biosynthetic steps set each stereocentre, and how precisely; and whether a synchronous species uses the antipode. Each explanation is supported by some systems, contradicted by others and untested in many. Resolving their relative importance will require comparative studies within clades that combine behaviour, receptor physiology and enzymology. Such studies would also tell practitioners, in advance, which pheromones can be deployed as cheaper stereoisomeric mixtures.

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851 *Use of Artificial Intelligence.* We used a generative AI tool to check statements against the cited
852 sources and to assist with revising the text. The authors reviewed and edited all content, verified
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856