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A combinatorial approach to the identification of self-assembled ligands for rhodium-catalysed asymmetric hydrogenation

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An effective and efficient means to catalyst discovery is the high-throughput screening of catalyst libraries. However, the current status of this approach suffers from a number of limitations, namely access to structurally diverse and meaningful ligand libraries and the enormous effort required for massive parallel screening of the resulting catalysts. We report an integrated solution to these drawbacks, which combines a diversity-oriented ligand synthesis, a catalyst-generation process driven by self-assembly and, finally, a combinatorial iterative library deconvolution strategy to identify the optimal catalyst. As a test case, rhodium-catalysed asymmetric hydrogenation was studied and, from a library of 120 self-assembling catalysts, highly enantioselective catalysts for the asymmetric hydrogenation of different olefinic substrates were identified within 17 experiments. Comparison of the results of the iterative library deconvolution strategy with those of the classic parallel-screening process confirmed the validity of this approach.

Asymmetric hydrogenation is the most important industrial application of asymmetric transition-metal catalysis, and has initiated substantial research activity in academia[1–3]. A remaining task of industrial importance in this field is the quest for rapid identification of an effective enantioselective molecular catalyst for a particular substrate[4,5]. Despite enormous efforts and significant progress in theoretical chemistry, it is still impossible to predict the optimal catalyst because the energy differences between the competing transition states involved are rather small given the complexity of the systems[6,7]. Thus, catalyst identification is still a process of trial and error and is driven by intuition, extensive labour and serendipity[5]. However, the catalyst-discovery process can be accelerated significantly if combinatorial methods are applied[4,5,8–18]. This approach was hampered by limited access to structurally diverse and meaningful ligand libraries, a problem that is crucial for the important classes of bidentate ligands. As a solution to this problem, recently we[19–28] and others[29–36] introduced an alternative to the classic covalent bidentate ligand synthesis; this alternative synthesis relies on the self-assembly of monodentate ligands through complementary hydrogen bonding in the presence of a metal salt to furnish defined heterobidentate ligand–metal complexes (Fig. 1).

Inspired by the A·T base pair in (deoxy)ribonucleic acid (DNA), we developed an analogous self-assembling aminopyridine (**1**, L^{AD} ligand)–isoquinolone (**3**, L^{DA} ligand) system[20], which was extended recently to other heterocyclic self-assembly platforms such as the thiazoles (**2**, L^{AD} ligands) and azaindoles (**4**, L^{DA} ligands)[27]. The approach is intrinsically combinatorial because, from a set of m L^{AD} ligands and n L^{DA} ligands, we can generate catalysts, without any synthetic steps, simply by mixing a library of $m \times n$ heterobidentate complexes. We provided proof-of-principle for this concept and identified excellent catalysts for the regioselective hydroformylation[20,27] and hydrocyanation[28] of alkenes, the anti-Markovnikov water addition to alkynes[23] and achieved preliminary and promising results in asymmetric rhodium-catalysed hydrogenation[25]. In all these cases, the best catalyst was identified by testing each metal–heterobidentate ligand combination individually. However, a significant advance would be to identify the best catalyst directly from a mixture of all individual catalysts formed through combinatorial self-assembly[37,38].

We herein report the realization of this concept in the context of asymmetric rhodium-catalysed hydrogenation, and demonstrate the full power of our approach for (1) diversity-oriented and combinatorial ligand synthesis, (2) combinatorial catalyst preparation through self-assembly on mixing of the individual complementary ligands in the presence of a catalytically active metal salt and (3)

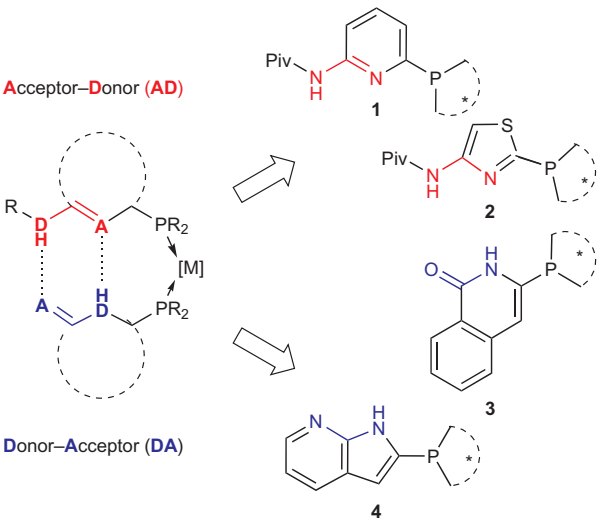

Figure 1 | Self-assembly of bidentate ligands by DNA-inspired complementary hydrogen bonding. Two sets of monodentate ligands with donor–acceptor (DA) and acceptor–donor (AD) hydrogen-bonding units were designed. Hydrogen bonding between complementary pairs results in the formation of a pseudo-bidentate ligand. Piv = pivaloyl; ⋆ = chiral backbone.

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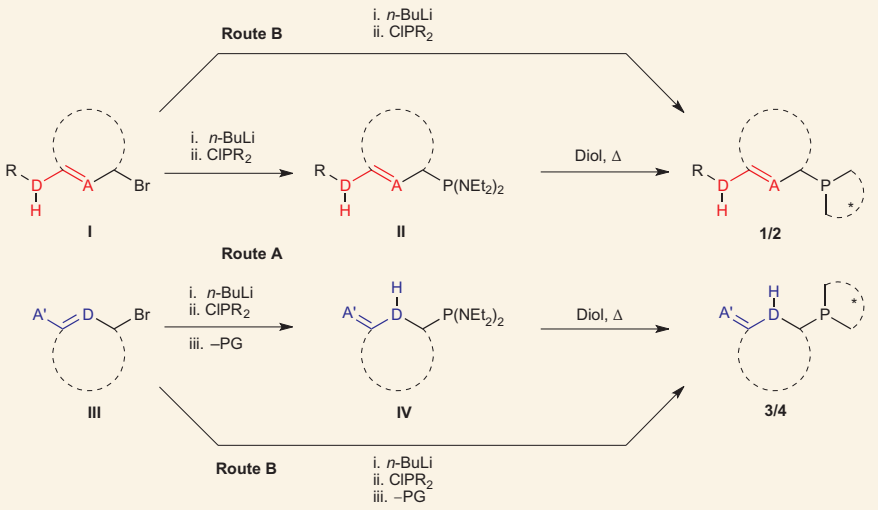
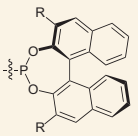
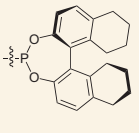
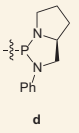
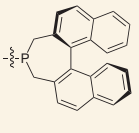
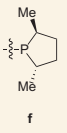
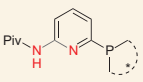
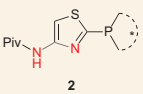
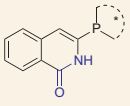
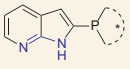
Table 1 | Combinatorial synthesis of the AD and DA ligands.



=	 **a** (R = H) **b** (R = Me)	 **c**	 **d**	 **e**	 **f**
 **1**	**1a** (79%) **1b** (83%)	**1c** (75%)	**1d** (75%)	**1e** (69%)	**1f** (84%)
 **2**	**2a** (88%) **2b** (92%)	**2c** (85%)	**2d** (75%)	**2e** (83%)	**2f** (70%)
 **3**	**3a** (92%) **3b** (90%)	**3c** (85%)	**3d** (95%)	**3e** (81%)	**3f** (76%)
 **4**	**4a** (80%) **4b** (72%)	**4c** (79%)	**4d** (63%)	-	-

n-BuLi = *n*-butyllithium, PG = protecting group; Δ = thermal treatment; $ClPR_2$ = dialkylchlorophosphine.

identification of the best catalyst from a mixture of catalysts using strictly combinatorial methods.

Results and discussion

Divergent ligand library synthesis. The diversity-oriented ligand synthesis started from the corresponding bromine-functionalized heterocycles **I** and **III** (Table 1). Key intermediates were the bisdiethylaminophosphines **II** and **IV** (ref. 25). Thus, simple heating with an appropriate chiral diol or diamine allowed the rapid preparation of a diverse set of phosphonites and diazaphosphanes (route A, Table 1). A second group of ligands, chiral phosphepines[24] and phospholanes[24], was prepared in a single step starting from the heteroarylbromides **I** and **III** (route B, Table 1). Thus, with this late-stage installation of the chiral P-donors in just a few synthetic steps a 12 × 10 ligand matrix was generated rapidly.

Asymmetric hydrogenation. With this library of 12 × 10 ligands available, catalyst evaluation for the rhodium-catalysed asymmetric hydrogenation was necessary. To identify the most effective catalyst for this reaction, the classic approach is to investigate all of the 120 possible combinations individually. However, it is a time- and resource-consuming endeavour to screen 120 combinations for one reaction, substrate and conditions, and such an approach is only efficient if automation is possible. Thus, if the technical prerequisites for automated

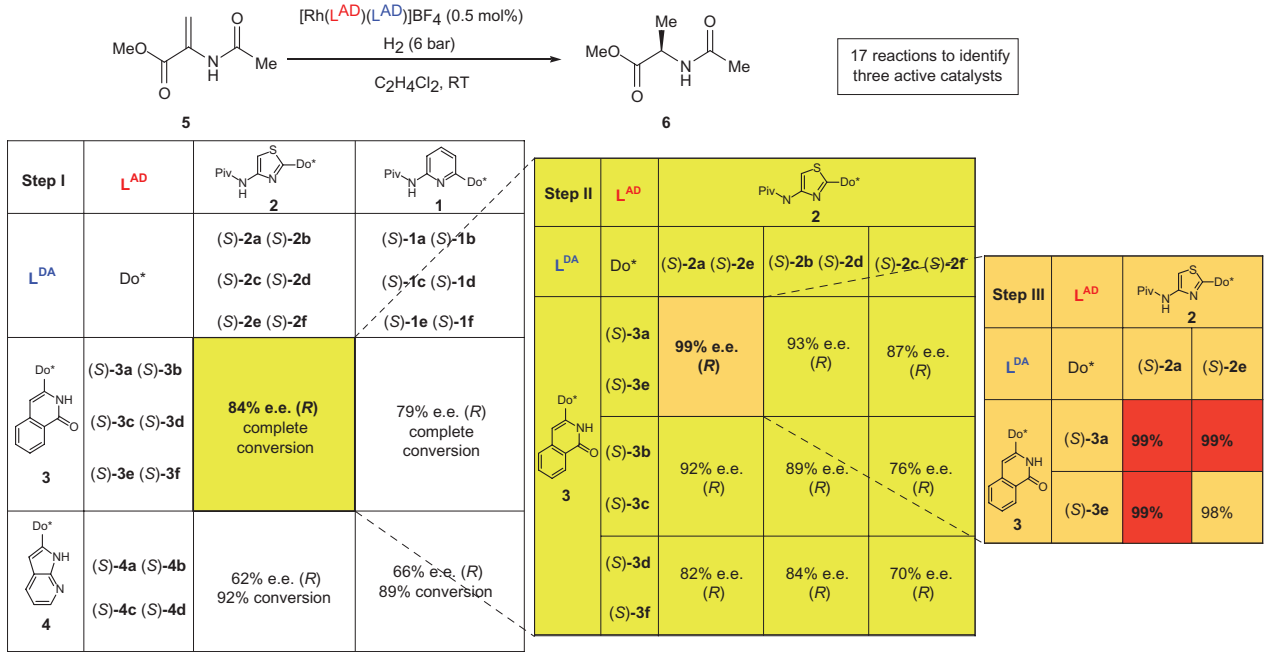


Figure 2 | Combinatorial approach to the identification of the most active and selective ligand combination(s). Reaction conditions: $[Rh(nbd)_2]BF_4$, $[Rh]:L^{AD}:L^{DA}$:substrate = 1:1.05:1.05:200, 6 bar H_2, dichloroethane, initial concentration of substrate = 0.3 M, 12 hours. The enantioselectivity was determined by chiral stationary-phase GC (see Supplementary Information). After a reaction time of 12 hours, conversion was determined by ^{1}H NMR spectroscopy. Do* = chiral P-donor substituent, RT = room temperature.

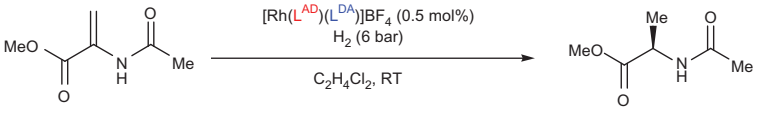
screening are not available a practical and efficient alternative that avoids the testing of all possible 120 combinations individually is highly desirable.

When 22 monodentate ligands are mixed with a metal salt, the formation of 253 catalytically active ML_2 species is theoretically possible. However, the self-assembling ligand library limits this number to 120 because of the preference for complementary hydrogen-bonding between matching ligand pairs. Thus, an ideal scenario is to mix all 22 ligands in the presence of a rhodium precursor and to run the catalysis with this 120-catalyst library. The problem is, however, to identify the best catalyst from such a combinatorial catalyst mixture, which resembles the search for a needle in a haystack.

Iterative deconvolution screening strategy. As a solution to this problem we propose the application of an iterative deconvolution strategy. The first step of this strategy is the division of this library of self-assembling ligands into subgroups. For each subgroup the complete combinatorial mixture of possible rhodium catalysts is generated and this mixture of catalysts evaluated for catalyst activity and selectivity. The ligand subgroup with the best results in terms of the catalyst outcomes is deconvoluted further by division into new subgroups and evaluation as catalysts, and all the other subgroups of catalysts are neglected. This process is repeated until the most active and selective catalyst is identified. Of course, with this strategy less active but enantioselective catalysts are not found. However, in practice – when expensive noble-metal catalysts and ligands are involved – it is more desirable to identify catalysts that are both highly active and highly selective to allow low catalyst loadings. In addition, a time-consuming and expensive factor that should not be ignored is the analysis of the reactions. With this strategy, it is not only possible to reduce the number of reactions to be run, but also to reduce the number of gas chromatography (GC) or high-performance liquid chromatography (HPLC) analyses to the same extent. For the strategy to work in practice two prerequisites have to be met by the catalyst libraries. First, on mixing m ligands L^{AD} with n ligands L^{DA} in the presence of a metal salt all possible heterocombinations must form in similar concentrations. Second, the individual self-assembled catalysts must not interfere with each other, but must perform independently.

The 120-catalyst library was divided into four subgroups (two of 36 and two of 24 catalysts) on the basis of the individual self-assembly platforms (Fig. 2, step I). The four catalyst libraries were generated through simple mixing of the components. The amount of rhodium catalyst used for all four experiments was 0.5 mol%. The substrate *N*-acetamidoacrylate (**5**) was selected and all the reactions were run at 6 bar hydrogen pressure for 12 hours. All four reaction mixtures were analysed by GC to determine the conversion and enantioselectivity of the four catalyst mixtures. The results are given in Fig. 2, step I. The results with catalyst libraries based on the azaindole system **4** were mediocre in terms of enantioselectivity and activity, and the best results were obtained with the catalyst libraries based on the isoquinolone system **3**. Both the combination with aminopyridine **1** and the combination with thiazole systems **2** furnished catalyst systems that gave complete conversion. However, the thiazole **2** catalyst library achieved a higher enantioselectivity (84% enantiomeric excess (e.e.)). For this reason, after our iterative deconvolution strategy we focused on this catalyst library (**2**/**3** rhodium systems) for step II. Through this selection process, the original number of catalysts decreased from 120 to 36! In step II, subgroup division was made on the basis of steric demand of the individual donor ligands. As such, we selected the nine subgroups displayed in Fig. 2, step II.

All nine subgroups of the catalyst libraries were generated and employed as in step I for the asymmetric hydrogenation of **5**. With all nine subgroups of catalysts, quantitative conversions were achieved, but the enantioselectivities were significantly different (Fig. 2, step II). Clearly, the best catalyst family formed from the combination of L^{AD} ligands **2a** and **2e** with the L^{DA} ligands **3a** and **3e**, with 99% e.e. Step II reduced the original 120-catalyst library to four potential candidates. In step III these four combinations were examined individually during the course of the asymmetric hydrogenation of **5**, again under identical conditions to those used for steps I and II. From these four combinations, three (**2a**/**3a**,



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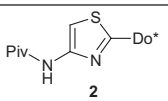
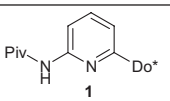
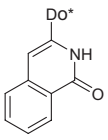
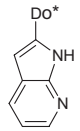
	L^{DA}	 2						 1					
L^{DA}	e.e. (conv.)	(*S*)-**2a**	(*S*)-**2b**	(*S*)-**2c**	(*S*)-**2d**	(*S*)-**2e**	(*S*,*S*)-**2f**	(*S*)-**1a**	(*S*)-**1b**	(*S*)-**1c**	(*S*)-**1d**	(*S*)-**1e**	(*S*)-**1f**
 3	(*S*)-**3a**	**99 (quant.)**	96 (quant.)	95 (quant.)	88 (quant.)	**99 (quant.)**	79 (quant.)	**99 (86)**	97 (88)	96 (89)	89 (quant.)	**99 (90)**	81 (93)
	(*S*)-**3b**	90 (quant.)	91 (99)	90 (98)	92 (quant.)	90 (quant.)	84 (quant.)	92 (84)	89 (86)	91 (85)	86 (89)	93 (86)	85 (94)
	(*S*)-**3c**	94 (quant.)	82 (98)	88 (97)	90 (quant.)	95 (quant.)	88 (quant.)	94 (83)	93 (79)	87 (78)	88 (81)	90 (84)	81 (85)
	(*S*)-**3d**	92 (quant.)	88 (quant.)	81 (quant.)	66 (quant.)	91 (quant.)	60 (quant.)	89 (quant.)	84 (98)	85 (95)	54 (90)	88 (quant.)	40 (88)
	(*S*)-**3e**	**99 (quant.)**	94 (quant.)	92 (quant.)	89 (quant.)	98 (quant.)	90 (quant.)	**99 (89)**	98 (87)	94 (86)	84 (95)	**99 (92)**	79 (95)
	(*S*)-**3f**	87 (quant.)	89 (quant.)	90 (quant.)	80 (quant.)	88 (quant.)	78 (quant.)	93 (quant.)	95 (95)	94 (89)	81 (95)	89 (87)	74 (83)
 4	(*S*)-**4a**	90 (quant.)	87 (94)	90 (92)	41 (96)	91 (quant.)	76 (53)	88 (85)	87 (78)	91 (81)	46 (84)	87 (90)	79 (47)
	(*S*)-**4b**	82 (quant.)	77 (72)	85 (57)	49 (80)	81 (quant.)	39 (15)	84 (81)	83 (80)	89 (59)	55 (73)	85 (81)	48 (58)
	(*S*)-**4c**	78 (quant.)	66 (89)	74 (35)	37 (77)	79 (quant.)	36 (14)	80 (82)	71 (71)	77 (656)	49 (68)	82 (85)	20 (64)
	(*S*)-**4d**	81 (quant.)	81 (84)	84 (66)	52 (98)	82 (quant.)	43 (56)	83 (88)	82 (58)	86 (67)	38 (quant.)	80 (87)	44 (78)

Figure 3 | Parallel screening of a library of 120 self-assembled catalysts—the classic approach. Reaction conditions: $[Rh(nbd)_2]BF_4$, [Rh]:L^{AD}:L^{DA}:substrate = 1:1.05:1.05:200, 6 bar H_2, dichloroethane, initial concentration of substrate = 0.3 M, 12 hours. Enantioselectivity was determined using chiral stationary-phase GC (see Supplementary Information), and after 12 hours of reaction time the conversion was determined by ^{1}H NMR spectroscopy. In all cases, ligand combinations with the same absolute configuration were chosen because control experiments showed that ligand combination with the opposite absolute configuration led to mismatched cases (see Supplementary Information Chapter 5). The highlighted results indicate that the same combinations of ligands were identified using the combinatorial approach.

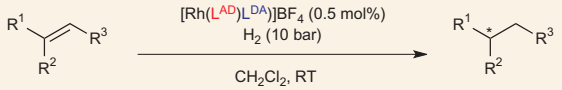
2a/**3e** und **2e**/**3a**) displayed 99% e.e. for the formation of (*R*)-*N*-acetylaminopropionic acid methyl ester **6**. Thus, applying this iterative deconvolution strategy we reduced the number of catalyst tests for a 120-catalyst library from 120 to a total of 17 reactions, which allowed us to identify three individual self-assembled catalysts that all operated with quantitative conversions and excellent enantioselectivity.

Classic parallel screening. However, at this point the question arose as to whether the results obtained from this iterative deconvolution of the 120-catalyst library would be the same as those when all 120 catalysts are screened individually. Thus, finally we undertook an individual screen of all 120 self-assembled catalysts for the hydrogenation of **5** under identical conditions, as used in steps I to III (Fig. 2). The results are given in Fig. 3.

Indeed, the same three optimal catalysts based on the thiazole system **2** were found to be the best catalysts and displayed both highest activity and most enantioselectivity. Additionally, in the aminopyridine **1**/isoquinolone **3** quadrant four other self-assembled catalysts were identified that also performed with enantioselectivities of 99% e.e. (**1a**/**3a**, **1a**/**3e**, **1e**/**3a** and **1e**/**3e**). Not surprisingly, these catalysts displayed the same P-donor units as those found in the thiazole **2**/isoquinolone **3** quadrant. However, the aminopyridine catalysts were less active. Thus, the iterative deconvolution strategy is capable of identifying, in a rapid manner, the most active and selective catalysts from this library of self-assembling catalysts. So, the originally proposed prerequisite as to whether these self-assembling catalysts do operate individually and also within a mixture of other self-assembling catalysts is obviously fulfilled. Otherwise the iterative deconvolution approach and the parallel screening of all individual catalysts would not have led to the identification of the same optimal catalysts.

To test whether this approach is more general we applied the same iterative deconvolution strategy with the same 120-catalyst library to substrates **7**, **8**, **9** and **10** (Table 2; for details see the Supplementary Information). In all cases the deconvolution strategy provided an optimal catalyst after 17 experiments in each individual substrate case. Notably, depending on the substrate, the optimal self-assembly catalyst may vary significantly in molecular structure. Thus, for the phenylalanine precursor **7** two *ortho*-methyl substituents at the binaphthol (binol) skeleton of the isoquinoline-based ligand **3a** proved important. For the β-branched amino acid

Table 2 | Identification of the optimal ligand combination for different alkene substrates.



Substrate	Ligand L^{DA}	Ligand L^{AD}	Enantiomeric excess (%)		
			$L^{DA} \times L^{DA}$	$L^{AD} \times L^{AD}$	$L^{DA} \times L^{AD}$
7	3b	2a	73 (*R*)	93 (*R*)	99 (*R*)
8	3e	2a	89 (*R*)	92 (*R*)	99 (*R*)
9	3f	2a	79 (*S*)	90 (*S*)	99 (*S*)
10	4a	2a	73 (*R*)	88 (*R*)	96 (*R*)

Reaction conditions: $[Rh(nbd)_2]BF_4$, $[Rh]:L^{AD}:L^{DA}$:substrate = 1:1.05:1.05:200, 6 bar H_2, dichloroethane, initial concentration of substrate = 0.3 M, 12 hours. Enantioselectivity was determined using chiral stationary-phase GC (see Supplementary Information), and after 12 hours of reaction time the conversion was determined by ^{1}H NMR spectroscopy. In all cases, the heterocombinations of ligands provided significantly higher enantioselectivity than the corresponding homocombinations, which proves the self-assembling catalysts to be the kinetically active species. Phth = phthaloyl.

precursor **8** a phosphepine **3e**/phosphinite **2a** combination was the most efficient, although for the itaconate system **9** a phospholane **3f**/phosphinite **2a** catalyst was best. For substrates **7**, **8** and **9** the isoquinolone/thiazole self-assembly platform provided the best results in catalysis, but for the enamide substrate **10** the azaindole **4a**/thiazole **2a** platform proved better. Thus, there is no single catalyst for all substrates. However, there is a focused self-assembling ligand library that allows, through this iterative deconvolution screening process, the rapid identification of the optimal catalysts for many substrates. This approach should accelerate significantly the catalyst discovery and optimization process and should find wide application beyond asymmetric hydrogenation.

Methods

General procedure for asymmetric hydrogenation. $[Rh(norbornadiene)_2]BF_4$ ($[Rh(nbd)_2]BF_4$) (5.0×10^{-3} mmol, 1.0 mol%), ligand L^{AD} (5.25×10^{-3} mmol, 1.05 mol%) and ligand L^{DA} (5.25×10^{-3} mmol, 1.05 mol%) were dissolved in 1,2-dichloroethane (5 ml) and stirred at room temperature for 30 minutes. Subsequently, the appropriate substrate (0.5 mmol, 1.0 equivalent) was added in one portion. For hydrogenations performed at higher pressures, the reaction mixture was transferred by syringe into a steel autoclave equipped with a glass inlet and under an argon atmosphere. The reaction mixture was saturated with hydrogen gas by applying four cycles of careful evacuation and refilling with hydrogen gas followed by adjustment of the reaction pressure indicated. The reaction was stirred magnetically at room temperature for 12 hours. Subsequently, the autoclave was depressurized and the reaction mixture was analysed by GC and HPLC.

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Author contributions

J.W. and B.B. conceived and designed the experiments. J.W. performed the experiments. J.W. and B.B. co-wrote the paper.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/. Correspondence and requests for materials should be addressed to B.B.