Graphical abstract

Recent trends and developments in the asymmetric synhesis of profens

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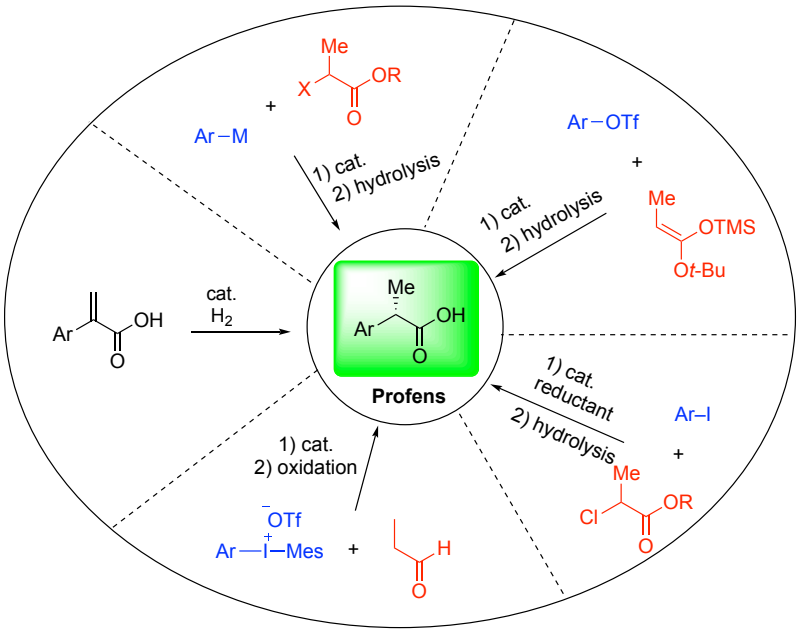

2-Arylpropionic acid derivatives, known as profens, are non-steroidal anti-inflammatory drugs (NSAIDs) that have been used clinically for over 50 years. This review outlines historically important and recent efforts for the enantioselective synthesis of these important medications.

Review

Recent trends and developments in the asymmetric synthesis of profens

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ABSTRACT

The profens belong to a class of nonsteroidal anti-inflammatory drugs (NSAIDs), which exert significant anti-inflammatory, analgesic, antipyretic and other pharmacological effects. A considerable number of catalytic asymmetric strategies for the synthesis of enantioenriched profens have been introduced. Herein are outlined recent trends and developments of promising catalytic enantioselective systems for the generation of profens and their derivatives. According to the reaction type, we divided these transformations into three categories: Transition metal-catalyzed asymmetric hydrogenations, transition metal-catalyzed asymmetric cross-couplings and organocatalytic asymmetric transformations. Overviews of generic reaction mechanisms are presented. Ideally, this tutorial review will motivate further interest in the catalytic asymmetric synthesis of highly enantioenriched profens.

1. Introduction

The profens, which are 2-arylpropionic acid derivatives, are non-steroidal anti-inflammatory drugs (NSAIDs) that have been used clinically for over 50 years[1]. Profens are used for treating osteoarthritis, rheumatoid arthritis, and to reduce blood clotting and fever due to their anti-inflammatory, anti-rheumatic and analgesic therapeutic effects[2-4]. Different profens can lead to distinct side effects[5]. These, of course, are dependent on the drug structure, dose and length of use, and can include gastrointestinal bleeding and ulcers,[6] kidney disease[7, 8] and heart attacks[9, 10]. Most profens are available in racemic form (with ibuprofen and ketoprofen now sold in enantioenriched form, joining naproxen, which was always available as a single enantiomer)[11]. Pharmacological mechanistic studies indicate the anti-inflammatory effect is achieved by inhibiting the cyclooxygenase (COX) activity, which produces the prostaglandins and thromboxane TXA2[12]. Further efforts verified that the (*S*)-enantiomer displays anti-inflammatory activity[13] and the (*R*)-enantiomer can be racemized enzymatically, although the extent of this inversion varies depending on the drug and the individual[14] (at patient-dependent rates). For example, the *R*-enantiomer of fenoprofen is racemized, whereas very little *R*-ketoprofen or *R*-flurbiprofen undergoes racemization[15, 16]. Early debate centered on the impact of the side effects of the (*R*)-enantiomer and the different pharmacokinetics of racemic mixtures[17]. Based on these key studies, the production of enantiopure (*S*)-profens, such as ibuprofen, naproxen, and ketoprofen, among others, is preferred (Fig 1). Several approaches have been used to access enantioenriched (*S*)-profens. The traditional approach to obtain the (*S*)-profen family was to employ enantioenriched precursors, which led to high costs [18-23]. Another traditional protocol that is still used employs classical resolutions and recycling the less active (*R*)-enantiomer by racemization[24]. Recently, promising progress has been made on kinetic resolutions,[25, 26] selective crystallizations and in situ racemization[27]. The third strategy to form the (*S*)-profen family of bioactive compounds is directly from achiral or racemic substrates *via* asymmetric catalysis. Clearly, the asymmetric catalysis strategy is the most promising approach, although it can be more challenging to develop. Nonetheless, tremendous efforts have been expended in the area of enantioselective synthesis using enantioenriched small molecule catalysts[28].

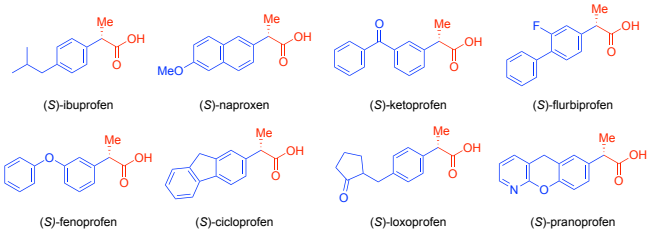


Fig 1. The structure of common (*S*)-profens.

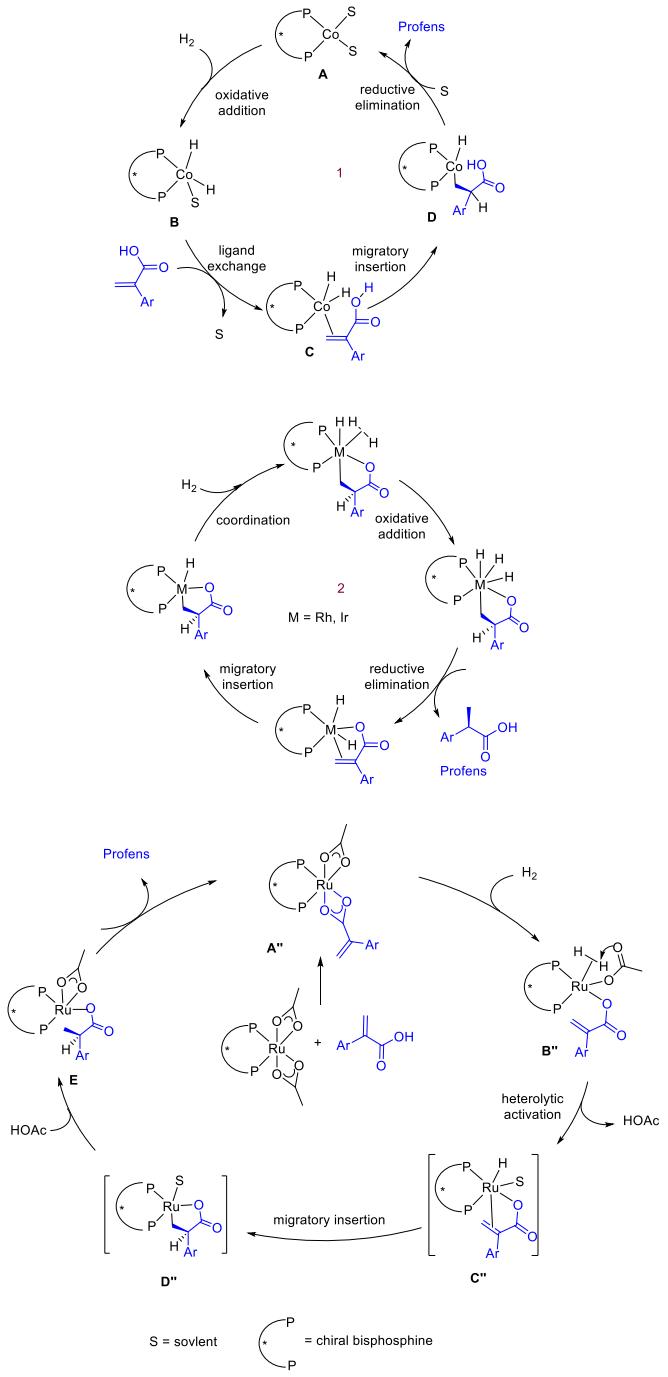
The subject of the synthesis of enantioenriched profens has not been reviewed recently. In 2011, Kourist, Domínguez de María and Miyamoto published a review on biocatalytic strategies for the asymmetric synthesis of profens[29]. Key to the success of these biocatalysts is the impressive developments in enzyme discovery and protein engineering. We are not aware, however, of reviews focusing on homogeneous small molecule transition metal catalysis or organocatalysts. In this critical

review, we present a systematic and comprehensive summary of the asymmetric synthesis of (*S*)-proxen and/or their derivatives *via* metal and organocatalyzed processes. The review is presented according to the nature of the reaction and catalysts used. It is divided into three categories: transition metal (TM)-catalyzed asymmetric hydrogenations, TM-catalyzed asymmetric cross-couplings and organocatalytic syntheses. Each section describes the advantages, limitations and applications of the approaches in detail. In particular, contributions that merit further development and those that exhibit high enantioselectivity for (*S*)-proxen and/or their derivatives will be described. Generalities of the reaction mechanisms will be presented that contain the key steps for context and edification of those new to these reactions.

2. TM-catalyzed asymmetric hydrogenation

TM-catalyzed asymmetric hydrogenations (AH) of unsaturated carboxylic acids is one of the most straightforward and powerful strategies for the synthesis of enantioenriched profens. The enantioselectivity and efficiency of asymmetric TM catalysis mainly depend on the nature of TM/enantioenriched ligand combinations. Other factors such as hydrogen pressure, substrates steric hindrance and solvent can also impact the enantioselectivity, sometimes in a dramatic fashion. Mechanistic studies indicate that the reactions proceed by different pathways depending on the metal involved and even the substrate. In the case of the Co-catalyzed AH, the reaction is believed to progress *via* the Cycle **1** pathway (Scheme 1). Chirik and co-workers demonstrated that the use of D_2 gives 1,2-di-deutero incorporation and no exchange with protic solvents[30]. Based on these experiments and others, we propose that Co(0) intermediate **A** undergoes oxidative addition of H_2 and ligand exchange to bind the unsaturated substrate. Migratory insertion is then followed by reductive elimination to afford the product and regenerate Co(0). It is not clear how the chelation of the acid is involved, but reactions with esters give lower conversions. In contrast to the cobalt catalysts, studies suggest that Rh and Ir-catalyzed AH tend to follow Cycle **2** (Scheme 1, right)[31-34]. Evidence to support this cycle includes 1) the migratory insertion H–Ir(III) intermediate was isolated, but did not undergo C–H reductive elimination in the absence of H_2 [35] (discounting an Ir^{I}/Ir^{III} couple) and 2) deuterium labeling studies performed by addition of D_2 to the migratory insertion H–Ir(III) intermediate similar to **B'** resulted in a hydrogenation product with 50% deuterium at the newly formed C−H/D bond. Thus, the reaction is believed to proceed by chelation of the α,β-unsaturated carboxylate to the Ir-dihydride to generate **A'** followed by migratory insertion to give **B'**. The binding of H_2 and oxidative addition forms the Ir(V) trihydride that undergoes reductive elimination. In the case of (BINAP)Ru-based catalysts, the reaction is initiated by (BINAP)$Ru(OAc)_2$ which undergoes exchange with the acid substrate. The reaction involves a heterolytic cleavage of H_2, as demonstrated by Halpern and Ashby[36]. These researchers showed that the use of D_2 in CH_3OH led to the incorporation of one equivalent of D in the product and one equivalent of H arising from the protonation of a Ru–C intermediate). Thus, as shown in Scheme 1, Cycle **3**, a possible reaction pathway involves the formation of a dihydrogen adduct and carboxylate-assisted cleavage of the bound H_2. The resulting mono-hydride complex likely chelates the C=C of the substrate followed by migratory insertion. Protonation of the Ru–C bond and exchange with fresh substrate generates the enantioenriched saturated acid. It is worth mentioning that the carboxylate group of the substrates plays a critical role in these TM-catalyzed AHs, presumably due to binding to the catalyst. For Ir-, Rh- and Ru-based catalysts, no hydrogenation occurs if the acids are replaced by their corresponding esters.

For the AH processes, four sections will be presented according to the TM employed, with studies outlined in chronological order. Examples of the successful synthesis of non-steroidal anti-inflammatory drugs will be tabulated for ease of comparison.



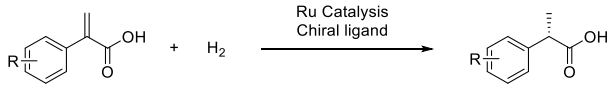
Scheme 1. Generic mechanisms for TMs-catalyzed asymmetric hydrogenation reactions.

2.1. Ruthenium-mediated asymmetric hydrogenations

In 1977, James and McMillan[37] reported ruthenium complexes of chelating (2*R*,3*R*)-2,3-*o*-isopropylidene-2,3-dihydroy-1,4-bis(methylsulfiny1)butane (**dios**) and an acetal-cleaved derivative (**ddios**), which were active homogeneous catalysts for AH of 2-phenylacrylic acid. The ligand is shown in Table 1 (entry 1). The configurations at sulfur of the sulfoxides were not known. Although the efficiency and enantioselectivity of this hydrogenation left much room for improvement (Table 1, entry 1, 17% conversion and 4% *ee*), the results served as a proof-of-concept for this potentially powerful strategy. Subsequently, the design and development of new chiral ligands with the potential to lead to excellent enantioselectivities and activities in the transition metal-catalyzed AH reaction was undertaken by many research groups. In 1987, Noyori[38] reported homogeneous catalysts, based on the Ru(BINAP) moiety, which was found to be highly effective in AH reactions (Table 1, entry 2). Noyori's team found that the extent of asymmetric induction was highly dependent on the hydrogen pressure. For example, when 2-phenylacrylic acid (atropic acid) was the substrate, the corresponding product was generated in 48% *ee* at 4 atm and in 92% *ee* at 112 atm. In the reduction to give (*S*)-naproxen, 92% yield and 97% *ee* were obtained at 135 atm (entry 2). Noyori was honored with the 2001 Nobel prize in chemistry for this and related seminal works[39]. In 1991, Schmid and coworkers[40] developed a prototypical axially chiral ligand, 6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine), abbreviated as MeO-BIPHEP (Table 1, entry 3). The methoxy groups are responsible for locking the stereochemistry of the biphenyl skeleton, which in turn influences the P–Ru–P bite angles and disposition of the diastereomeric P-Ar substituents. It is known that conformation of the P–M–P metallocycle of the ligand impacts both the reactivity and enantioselectivity[41, 42]. Chan and co-workers[43] employed MeO-BIPHEP in a Ru-catalyzed AH of 2-(6-methoxynaphthalen-2-yl) acrylic acid, giving the corresponding product, naproxen, with 100% conversion and 94% *ee* (Table 1, entry 3).

In 1994, Takaya and co-authors[44] introduced H_8-BINAP, which proved to be effective in Ru-catalyzed AH reactions (Table 1, entry 4). Compared to Ru-BINAP catalysts, the Ru-H_8-BINAP catalyst performed under milder conditions (lower hydrogen pressures, shorter reaction times and lower temperatures). Not surprisingly, it was demonstrated that the effect of hydrogen pressure on the level of enantioselection was substrate-dependent. Reduction to give (*S*)-ibuprofen gave 94% *ee* at 25 atm and 97% *ee* at 100 atm (Table 1, entry 4). In 2006, Albert Chan and co-workers[43] developed a series of new chiral diphosphine ligands (PQ-Phos **1-3**) and evaluated their dihedral angles by using Chem 3D MM2 modeling. As shown in Table 1, entry 5, the dihedral angles were controlled by the length and substitution patterns of the tethers. Somewhat surprisingly, a correlation between the bite angles and enantioselectivity in AH of 2-(6-methoxynaphthalen-2-yl) acrylic acid indicated that the dihedral angles did not correlate with the observed product ee values in this reaction. In 2016, Zhang and co-workers[45] developed a ruthenocenyl phosphino-oxazoline–ruthenium complex with dual catalytic centers (entry 6). This enantioenriched P,N-Ru complex was used as the catalyst for the AH (5 bar H_2, r.t. in MeOH) of 2-arylacrylic acids, giving the corresponding products in quantitative conversions and with up to 99.9% *ee* (Table 1, entry 6). This reaction can be performed on a gram-scale with low catalyst loading (up to 5000 S/C), demonstrating the potential for commercial viability. With this catalyst system, (*S*)-ibuprofen was obtained in 98% yield with 98% *ee* and (*S*)-naproxen formed in 97% yield with 97% *ee*.

Table 1.
Ruthenium-mediated AHs for the synthesis of enantioenriched profens using homogeneous catalysis.



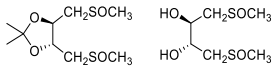
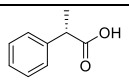
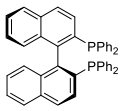
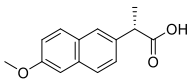
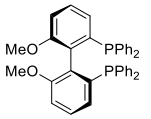
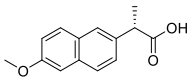
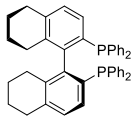
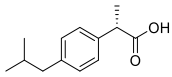
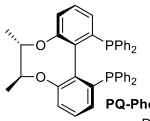
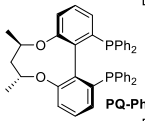
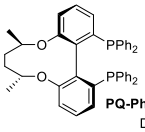
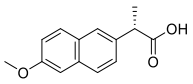
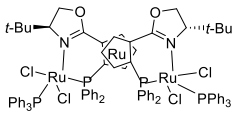
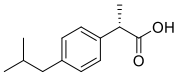
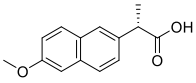
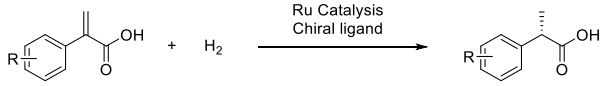
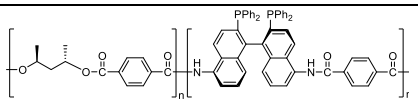
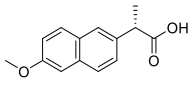
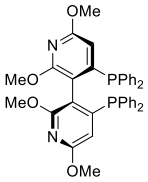
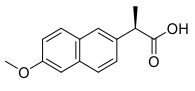
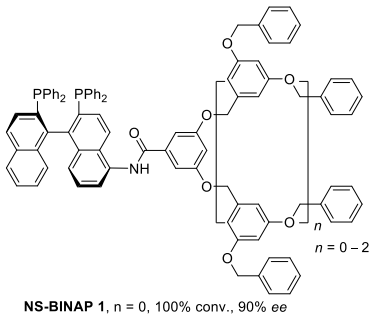
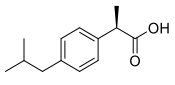
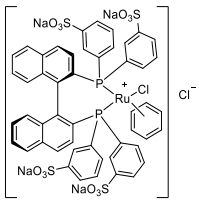
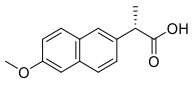
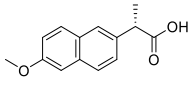
Entry	Rh Catalysis	Chiral ligand	Sub./cat. ratio	Examples
1	$RuCl_2$	 **dios** **ddios**	5	 17%, 4% *ee*
2	$Ru(OAc)_2$	 **BINAP**, 92%, 97% *ee*	215	 (*S*)-naproxen
3	$[Ru(p\text{-cymene})Cl_2]_2$	 **MeO-BIPHEP**, 100% conv., 94% *ee*	100	 (*S*)-naproxen
4	$Ru(OAc)_2$	 **H8-BINAP**, 97%, 97% *ee*	200	 (*S*)-ibuprofen
5	$[Ru(p\text{-cymene})\ Cl_2]_2$	 **PQ-Phos 1**, 100% conv., 97% *ee* Dihedral angles: 64.8°  **PQ-Phos 2**, 100% conv., 95% *ee* Dihedral angles: 80.0°  **PQ-Phos 3**, 100% conv., 95% *ee* Dihedral angles: 88.8°	100	 (*S*)-naproxen
6	Pre-catalyst	 **(*S*, *Sp*)-RuPHOX-Ru**	100	 (*S*)-ibuprofen, 98% yield, 98% *ee*  (*S*)-naproxen, 97% yield, 97% *ee*

Table 2.
Ruthenium-mediated AHs for the synthesis of enantioenriched profens using heterogeneous catalysis.



Entry	Rh Catalysis	Chiral ligand	Sub./cat. ratio	Examples
1	$[Ru(cymene)Cl_2]_2$	 **PS-BINAP**, 100% conv., 94% *ee*	200	 (*S*)-naproxen
2	Pre-catalyst Ru(*R*-P-phos)(acac)$_2$	 **P-phos,** 100% conv., 96% *ee*	200-800	 (*R*)-naproxen
3	$[RuC1_2(benzne)]_2$	 **NS-BINAP 1**, n = 0, 100% conv., 90% *ee* **NS-BINAP 2**, n = 1, 100% conv., 91% *ee* **NS-BINAP 3**, n = 2, 100% conv., 91% *ee*	100	 (*R*)-ibuprofen
4	Pre-catalyst Ru-sulphonated-BINAP	 Ru-sulphonated-BINAP held on controlled-pore glass, CPG-240, *via* aqueous-phase	100	 (*S*)-naproxen
5	Pre-catalyst Ru-BINAP	Immobilized in an ionic liquid phase	40	 (*S*)-naproxen

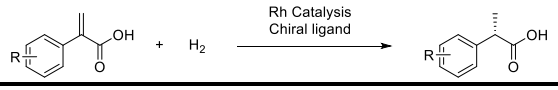
While these homogeneous catalyst systems are efficient and highly enantioselective, an obvious shortcoming is the separation of the catalyst from the reaction mixture and its recycling. To address this issue, in 1999 Albert Chan and co-workers[46] designed and developed a class of polymer-supported BINAP (PS-BINAP) ligands by using the concept of "one-phase catalysis and two-phase separation" (Table 2, entry 1). This polymer-supported BINAP ligand was used in the AH of 2-(6-methoxynaphthalen-2-yl) acrylic acid to naproxen by combining $[Ru(cymene)Cl_2]_2$ with the polymer-supported ligand. Not only did the polymer-supported enantioenriched catalyst show better catalytic activity (Table 2, entry 1, 100% conv., 93.6% *ee*) compared to the corresponding parent BINAP-based catalyst (94.7% conv., 93.5% *ee*), but it could also be separated and reused more than 10 times. The ease of separation was due to the different solubility of the chiral polyester-supported BINAP ligands in different solvents. Later, the same group developed an enantioenriched heteroaromatic BINAP analogue 2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine (P-phos) (Table 2, entry 2)[47]. The combination of ruthenium catalyst and P-phos offered high enantioselectivities in the catalytic hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid (96.2% *ee*). It is noteworthy that the separation of the pre-catalyst can be easily achieved by adjusting the acidity of the reaction mixture, because the pyridyl groups in P-phos ligands can be protonated to give cations. In 2002, Fan and co-workers[48] modified BINAP and developed a chiral dendritic ligand (NS-BINAP) in which the BINAP is located at the focal point of the nanoscale-sized dendrimer (Table 2, entry 3). The dendritic Ru-BINAP catalysts showed similar enantioselectivity compared to the parent Ru-BINAP catalyst in the catalytic AH

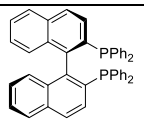
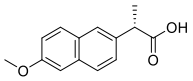
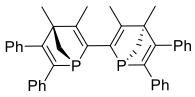
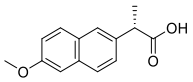
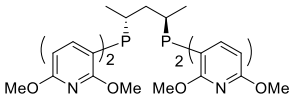
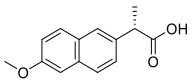
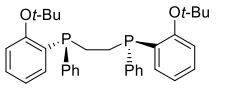
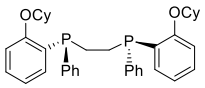
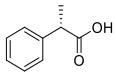
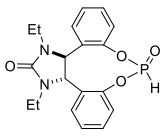
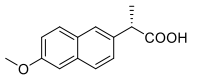
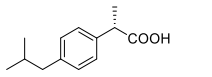
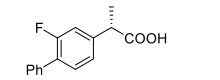
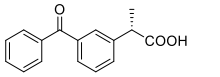
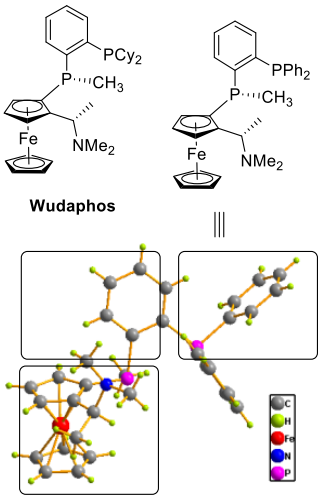
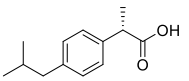
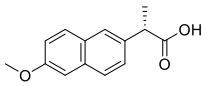
of 2-(4-isobutylphenyl)acrylic acid (90% vs. 91% *ee*). The key advantage of the dendritic catalyst was its ease of separation and reuse without any change in enantioselectivity through at least three cycles. The "heterogenization" of a homogeneous catalyst is another method to facilitate catalyst separation and recycling. In 1994, Wan and Davis[49] developed a supported aqueous-phase (SAP) catalyst, in which a water-soluble Ru-sulphonated-BINAP complex was held in a film of water on a porous hydrophilic support (controlled-pore glass, CPG-240) (Table 2, entry 4). Both the activity and enantioselectivity of this heterogeneous catalyst were impacted by the water content. Although, only about 70% *ee* was found in the AH of 2-(6-methoxynaphthalen-2-yl)acrylic acid to naproxen, the SAP catalyst was easily recovered without any leaching of ruthenium into the organic phase. Later, they found that ethylene glycol was a good substitute for water, and this modified version of the catalyst was comparable to the homogeneous analogue, giving 96% *ee* in the AH of 2-(6-methoxynaphthalen-2-yl)acrylic acid to naproxen[50]. In 1997, Dupont and coworkers[51] developed a new system for AH of 2-arylacrylic acids. In this system, the homogeneous catalyst Ru-BINAP was immobilized in an ionic liquid composed of 1-*n*-butyl-3-methylimidazolium tetrafluoroborate salt (BMI•BF_4). Isopropanol was used as a solvent to absorb all hydrogenation products at the end of the reaction (Table 2, entry 5). Key advantages of this approach were the quantitative separation of the product from the reaction mixture and the recovered ionic liquid phase containing the catalyst (which was reused several times without significant changes in the catalytic activity and enantioselectivity). A similar strategy was used by Jessop and coworkers in 2001[52]. The differences between these two works were that the latter employed an ionic liquid phase with 1-*n*-butyl-3-methylimidazolium hexafluoroborate and used supercritical CO_2 ($scCO_2$) to separate the product from the catalyst.

2.2. Rhodium-mediated asymmetric hydrogenations

Like ruthenium catalysts, rhodium complexes are also excellent catalysts for AH[53]. The enantioselectivities in rhodium-catalyzed reductions to make profens are highly dependent on the chiral ligands employed in these transformations. In 1991, Albert Chan reported an example of rhodium-catalyzed asymmetric hydrogenation for the synthesis of (*S*)-naproxen. BINAP was employed as a chiral ligand and the conversion was up to 100%, although the *ee* was only 73%[54] (Table 3, entry 1). In 1997, Mathey and co-workers[55] developed a new optically active bridgehead bisphosphine ligand (BIPNOR). The utility of BIPNOR was investigated by combination with Rh for the catalytic hydrogenation of 2-(6-methoxynaphthalen-2-yl)acrylic acid. The corresponding naproxen was formed with high ee values (98% *ee*), albeit with only 30% conversion (Table 3, entry 2). In 1998, Albert Chan and co-wokers[56] reported another chiral pyridylphosphine ligand (PyPhos), which was tested in the Rh-catalyzed AH of 2-(6-methoxynaphthalen-2-yl)acrylic acid. The naproxen was generated with 100% conv. and 56% *ee* (Table 3, entry 3). Based on the successful application by Knowles of his DiPAMP-based catalysts (1,2-bis[(*o*-anisyl)(phenyl)phosphino]ethane), in 2010, Stephan and coworkers[57] reported a series of 1,2-bis[(*o*-RO-phenyl)(phenyl)phosphino]ethane (R-SMS-Phos) ligands (R = *i*-Pr, *i*-Bu, *t*-Bu, 3-Pen and CH_2TMS). These R-SMS-Phos ligands were applied to the Rh(I)-mediated hydrogenation of olefins, including atropic acid, a model substrate for profens. The results indicated that *t*-Bu-SMS-Phos was the most successful of these ligands in the Rh(I)-mediated hydrogenation of atropic acid to hydratropic acid with 100% conversion and 96% *ee*. The conditions for this system were mild: 10 bar of H_2 at rt in MeOH, with reaction completion in 2 h in the presence of additives Cy_2NH (0.05 equiv) or Et_3N (0.05 equiv). Further study[58] showed that when R = Cy, the enantioselectivity of the hydratropic acid could reach 97% under the same conditions (Table 3, entry 4). In 2014, Ding and co-workers[59] reported a chiral monodentate secondary phosphine oxide (SPO) ligand which was used in Rh(I)-catalyzed AH of a wide variety of α-aryl acrylic acids. Several anti-inflammatory drugs, including (*S*)-naproxen (>99% conv., 95% *ee*), (*S*)-ibuprofen (>99% conv., 93% *ee*), (*S*)-flurbiprofen (>99% conv., 86% *ee*) and (*S*)-ketoprofen (>99% conv., 86% *ee*) were obtained under this catalytic system (Table 3, entry 5). It is noteworthy that the solvent played a key role in affecting the enantioselectivity. Aprotic solvents, especially toluene and dioxane, were ideal while protic solvents led to decreased enantioselectivities. In 2016, Zhang and Dong[60] reported a new class of enantioenriched ferrocenyl bisphosphine ligands, Wudaphos, with two bulky cyclohexyl substituents on one phosphorus center. The ligand had a chiral phosphorus center in the backbone and contained Ugi's amine moiety as well. As shown in Table 3 (entry 6) the ligand blocks three quadrants with the remaining quadrant open. The dimethyl amino unit in the ligand is proposed to play a key role in the high enantioselectivities of the catalyst through ion pair formation. Additionally, one bar of H_2 could be employed and no base was needed in this Rh mediated AH. Profens including (*S*)-ibuprofen (> 99% conv., 97% *ee*) and (*S*)-naproxen (> 99% conv., 99% *ee*) could be obtained with this system (Table 3, entry 6).

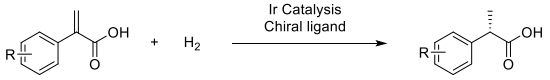
Table 3.
Rh-mediated AHs for the synthesis of enantioenriched profens

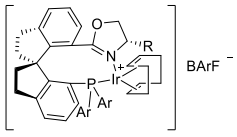
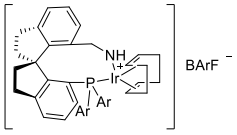
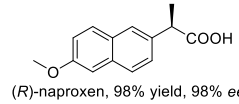
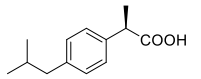
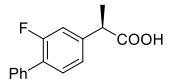
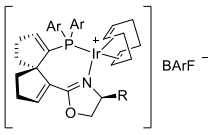
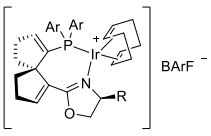
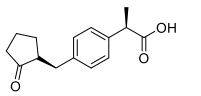


Entry	Rh Catalysis	Chiral ligand	Sub./cat. ratio	Examples
1	$[Rh(cod)_2]PF_6$	 **BINAP**, 100% conv., 73% *ee*	28	 (*S*)-naproxen
2	$[Rh(cod)_2]PF_6$	 **BIPNOR**, 30% conv., 98% *ee*	100	 (*S*)-naproxen
3	$[Rh(cod)_2]BF_4$	 **PyPhos**, 100% conv., 56% *ee*	100	 (*S*)-naproxen
4	$[Rh(nbd)_2]BF_4$	 **t-Bu-SMS-Phos**, 100% conv., 96% *ee*  **Cy-SMS-Phos**, 100% conv., 97% *ee*	100	
5	$[Rh(COD)Cl]_2$	 **SPO**	200	 (*S*)-naproxen, >99% conv., 95% *ee*  (*S*)-ibuprofen, >99% conv., 93% *ee*  (*S*)-flurbiprofen, >99% conv., 86% *ee*  (*S*)-ketoprofen, >99% conv., 86% *ee*
6	$[Rh(nbd)_2]BF_4$	 **Wudaphos**	100	 (*S*)-ibuprofen, 98% yield, 98% *ee*  (*S*)-naproxen, 97% yield, 97% *ee*

The iridium-catalyzed AH of olefins has emerged as a powerful tool in recent decades[61, 62]. Many examples of profen products have also been successfully prepared using iridium-based catalysts with enantioenriched ligands. Recent studies have shown that the AH proceed by homolytic oxidative addition of H_2, as shown in Scheme 1. In 2008, Zhou and co-workers[63] reported a [Ir(I)-SIPHOX] pre-catalyst in enantioselective hydrogenation of *α*,*β*-unsaturated carboxylic acids using their enantioenriched spiro phosphine oxazoline ligand (SIPHOX 1). Optimization studies indicated that increased steric hindrance on the phosphorus center had a positive influence on catalyst enantioselectivity and conversion while the substituent on the oxazoline ring had a minor impact. Based on these, and related experiments, they developed the chiral spiro aminophosphine ligand (SIPHOX 2) which showed high activity, with turnover numbers (TONs) up to 10000 and turnover frequencies (TOFs) up to 6000 h^{-1}. Excellent enantioselectivities (up to 99%) in the hydrogenation reaction were also observed[62]. Additionally, the AH could be conducted under one atmosphere of hydrogen gas at 45 ºC in MeOH, giving the saturated carboxylic acids in up to 99% yield and up to 99% *ee* [(*S*)-naproxen (98% yield, 98% *ee*), (*S*)-ibuprofen (98% yield, 99% *ee*) and (*S*)-ketoprofen (98% yield, 97% *ee*), Table 4, entry 1]. These outstanding results make this catalyst system potentially useful for industrial manufacturing. In 2010, Zhang and Ding[64] reported a class of chiral iridium(I) complexes, Ir-SpinPhox, with spirocyclic P,N ligands. The Ir complexes of these ligands were found to be highly efficient in AHs. A series of profen derivatives were obtained with the Ir(SpinPHOX 1)-catalyzed AH of *α*-aryl-*β*-substituted acrylic acids (Table 3, entry 2). In 2014, Ding and co-workers[65] employed a similar iridium(I) complex, Ir-SpinPHOX 2, to realize the AH of *α*-alkylidene lactams and/or lactones. The anti-inflammatory drug loxoprofen (98% yield, 82:18 d.r., 98% *ee*) was generated *via* a two-step AH of the acrylic and alkylidene C=C bonds in the (*E*)-2-(4-((2-oxocyclopentylidene)methyl)phenyl)acrylic acid (Table 4, entry 2).

Table 4.
Ir-mediated AHs for the synthesis of enantioenriched profens

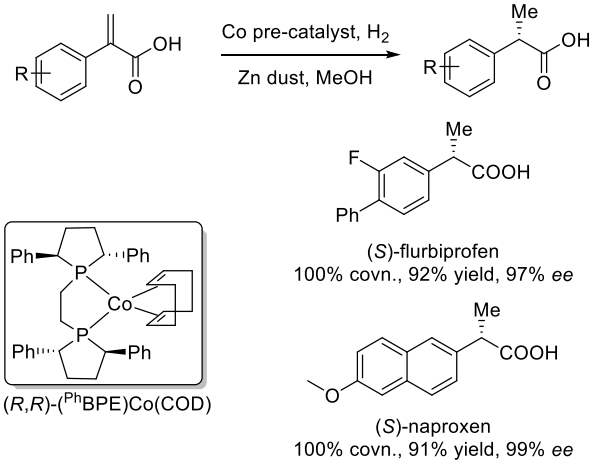


Entry	Ir Catalysis	Chiral ligand	Sub./cat. ratio	Examples
1	Pre-catalyst Ir(I)-SIPHOX	 **Ir-SIPHOX 1**, Ar = 3,5-*t*BuC$_6$H$_3$ R = Bn, Ph, ^{i}Pr, Me, H  **Ir-SIPHOX 2**, Ar = 3,5-*t*BuC$_6$H$_3$	400	 (*R*)-naproxen, 98% yield, 98% *ee*  (*R*)-ibuprofen, 98% yield, 99% *ee*  (*R*)-flurbiprofen, 98% yield, 97% *ee*
2	Pre-catalyst Ir(I)-SpinPHOX	 **Ir-SpinPHOX 1**, Ar = *o*-Tol R = Ph  **Ir-SpinPHOX 2**, Ar =Ph R = *s*Bu	100	 loxoprofen, 98% yield, 82:18 d.r., 98% *ee*

2.4. Cobalt-mediated asymmetric hydrogenations

The widespread utility of AH reactions, especially in industrial processes, has motivated efforts to develop less expensive earth-abundant TM catalysts to replace precious metals[66-68]. In 2018, Lu and co-workers[69] published a review on catalytic AH of prochiral olefins with earth-abundant first-row TMs, including titanium and cobalt. To our knowledge, the first example of first-row TM-catalyzed AH of *α*,*β*-unsaturated carboxylic acids to form profens was reported by Chirik and co-workers in 2020 using a cobalt catalyst (Scheme 2)[30]. They combined cobalt chloride [$CoCl_2 \cdot 6H_2O$] and (*R*,*R*)-

Ph-BPE {Ph-BPE = 1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane} to give a Co(II) species that was reduced with Zn metal to give the Co(0) precatalyst (COD)Co[(*R*,*R*)-(^{Ph}BPE)]. With this precatalyst, the hydrogenation reaction took place smoothly under 500 psi of H_2 at 50 ºC in MeOH, affording the saturated carboxylic acid in > 99% conversion and up to 99% *ee* (Scheme 2). Some examples of the products include (*S*)-naproxen (100% conv., 91% yield, 99% *ee*) and (*S*)-flurbiprofen (100% conv., 92% yield, 97% *ee*).



Scheme 2. Co-catalyzed AHs for the synthesis of enantioenriched profens.

3. TM-catalyzed asymmetric couplings

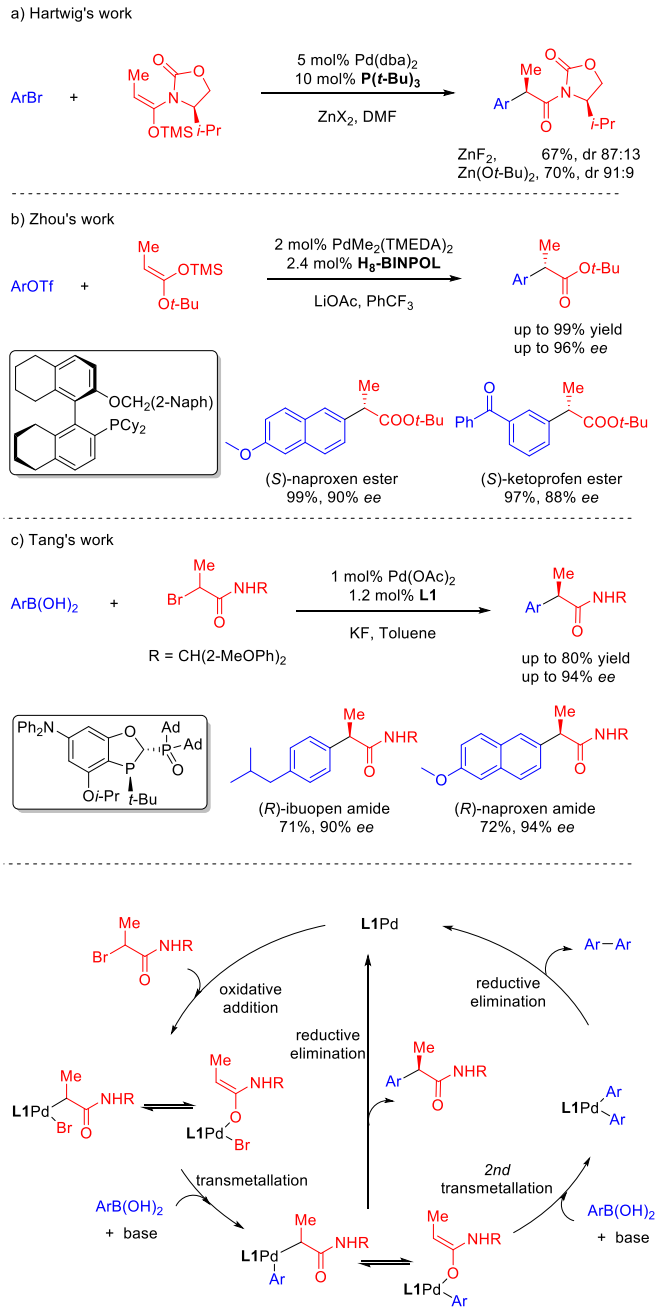
TM-catalyzed asymmetric cross-coupling reactions between two different coupling partners have emerged as powerful methods for the construction of enantioenriched products with tertiary and quaternary stereogenic centers[70]. Among these reactions, only a handful of examples exist for the direct synthesis of enantioenriched profens. The difficulty in these reactions is that substrates bearing carboxylic acids are challenging coupling partners because of their acidity. Enantioenriched profen derivatives, such as *a*-aryl esters and *a*-aryl amides, have been obtained *via* TM-catalyzed (Pd, Ni, Co, Fe and Cu) asymmetric couplings. The products of these reactions can be transformed to enantiopure profens *via* simple hydrolysis without loss of enantiomeric excess. A challenge in the TM-catalyzed asymmetric arylations of carbonyl compounds is that the monoarylation products contain an acidic α-hydrogen that can be easily deprotonated under basic conditions leading to racemization.

3.1. Palladium-catalyzed asymmetric cross-couplings for profen derivatives

Palladium-catalyzed cross-coupling reactions have been widely used in various fields[71]. Many chemists have contributed to these diverse and ubiquitous transformations. Given that stereoselective cross-coupling reactions form C–C bonds, the coupling approach has a potential advantage over enantioselective hydrogenations in that it is more convergent. Among Pd-catalyzed cross-coupling reactions, Hartwig's and Buchwald's groups have made great contributions in the synthesis of racemic and enantioenriched profen derivatives[72-76]. They independently developed a series of palladium-catalyzed α-arylations of carboxylic acid esters with aryl halides and pseudohalides. When trimethylsilyl enol ethers containing the Evans auxiliary were used, which is well known to control the stereochemistry of carbonyl derivatives, Hartwig and co-workers[73] discovered that the base-sensitive stereocenters were not epimerized in the presence of Zn(O-*t*Bu)$_2$ or ZnF_2 (Scheme 3a). This finding indicated that the arylation of silylenol ethers can potentially be employed to develop enantioselective α-arylation processes.

In 2011, Zhou and co-workers[77] reported a palladium-catalyzed asymmetric α-arylation of TMS-silyl ketene acetals with aryl triflates for the synthesis of enantioenriched profen derivatives (Scheme 3b). Both chiral monophosphine ligands derived from H_8-BINOL and the degree of steric hindrance of the silyl ketene acetals played key roles in determining the enantiomeric excess of the product. In this reaction, no racemization was observed because the weakly basic LiOAc used as an activator was not sufficiently basic to deprotonate α-arylesters. As a result, the (*S*)-naprofen ester (99%, 90% *ee*) and (*S*)-ketoprofen ester (97%, 88% *ee*) were obtained. It is noteworthy that only 2 mol% (TMEDA)PdMe$_2$ precatalyst and 2.4 mol% enantioenriched phosphine ligand were needed. Additionally, the reaction was scaled to produce 1.2 g of (*S*)-naproxen (92% *ee*), after acidic hydrolysis of the ester. Simple crystallization of the material from acetone–hexanes further improved the enantiomeric excess to 99%.

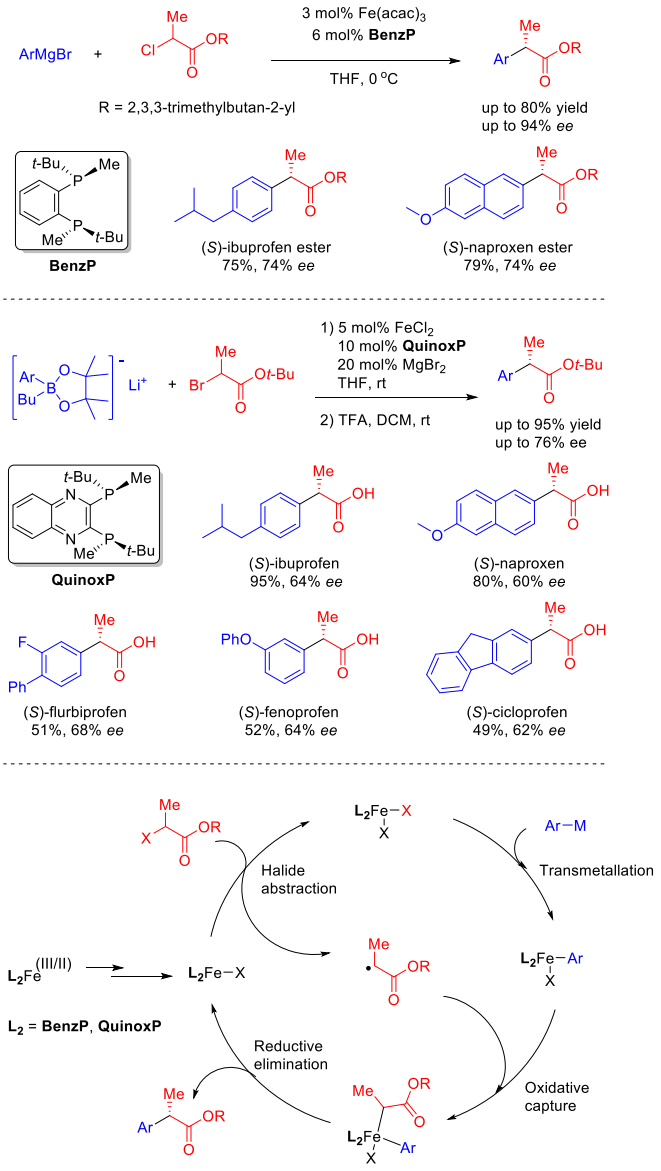
In 2019, Tang and co-workers[78] reported an enantioselective palladium-catalyzed Suzuki-Miyaura cross-coupling between racemic α-bromo carboxamides and arylboronic acids for the synthesis of enantioenriched profen derivatives (Scheme 3c). In the process, they developed a library of enantioenriched P-chiral phosphorous ligands[79] based on the dihydrobenzooxaphosphole backbone. A bulky phosphorus ligand (**L1**) was employed and exhibited high efficiency (up to 80% yield) and enantioselectivity (up to 94% *ee*) in the cross-coupling reaction. Additionally, the N-aryl group's steric hindrance played a role in increasing the ee. Enantioenriched profens such as ibuprofen (80%, 90% *ee*) and naproxen (85%, 93% *ee*) were obtained after acidic hydrolysis of the amide coupling products with 2 *N* HCl. Mechanistic investigations indicated that this cross-coupling followed a classic catalytic cycle (oxidative addition followed by transmetallation and reductive elimination). Bulky substituents on phosphorus played key role in inhibiting the 2nd transmetallation, subsequently leading to the generation of homocoupling byproduct.



Scheme 3. Palladium-catalyzed asymmetric cross-couplings for the synthesis of profens. The α-stereogenic center can be epimerized through the formation of the O-bound enolate.

3.2. Iron-catalyzed asymmetric cross-couplings for profen derivatives

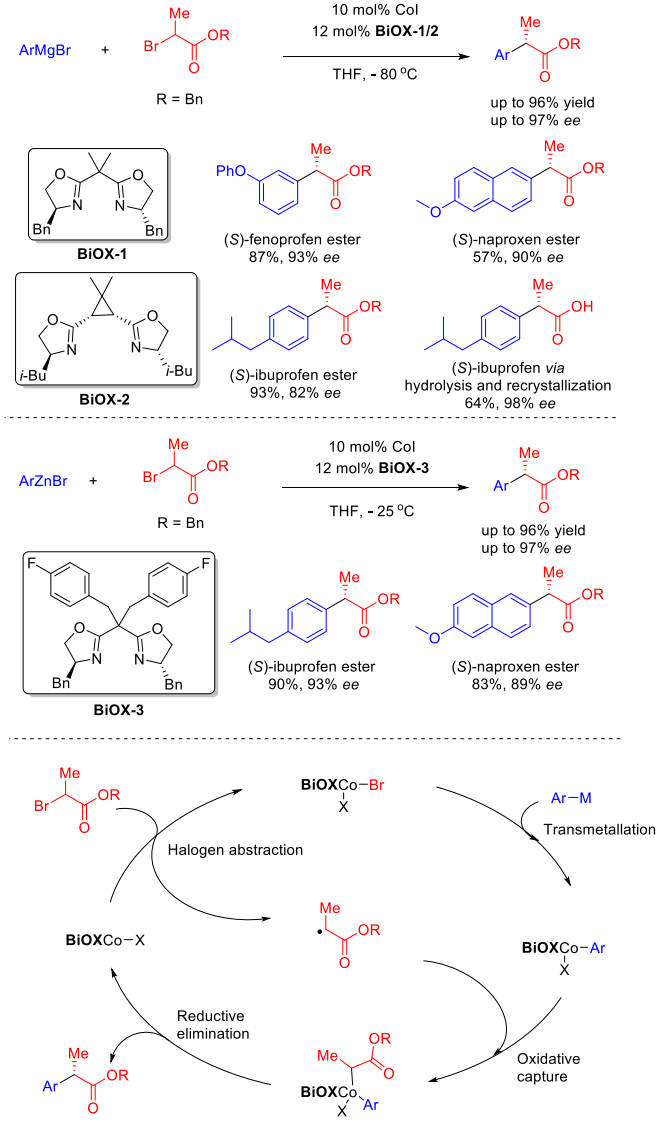
Recently, the use of earth-abundant and inexpensive TM catalysts supported by enantioenriched ligands to construct stereocenters has attracted much interest in the field of asymmetric catalysis[80-82]. In 2015, Nakamura and co-workers[83] reported the first iron-catalyzed enantioselective cross-coupling reaction between aryl Grignard reagents and α-chloroesters (Scheme 4). The combination of the enantioenriched phosphine ligand (BenzP), and the sterically demanding substrate OR group, were both necessary to favourably impact the enantioselectivity. Although this base-metal-catalyzed asymmetric Kumada reaction demonstrated a novel class of catalysts for the synthesis of enantioenriched profen derivatives, the yields and enantioselectivities left room for improvement. For example, the (*S*)-ibuprofen ester and (*S*)-naproxen ester were generated in 75% yield with 74% *ee* and a 79% yield with 74% *ee*, respectively. Nonetheless, this work served as inspiration for subsequent researchers using base-metal catalysts. Four years later, this team reported another example of iron-catalyzed enantioselective Suzuki–Miyaura coupling for the synthesis of optically active profens[84]. Compared to Benzp chiral ligand in their previous work, Quinoxp showed higher activity and enantioselectivity in this reaction. After simple hydrolysis with TFA, profens such as (*S*)-ibuprofen (95%, 64% *ee*), (*S*)-naproxen (80%, 60% *ee*), (*S*)-flurbiprofen (51%, 68% *ee*), (*S*)-fenoprofen (52%, 64% *ee*) and (*S*)-cicloprofen (49%, 62% *ee*) were formed without loss of optical purity. Mechanistic studies indicated[84] that these Fe-catalyzed asymmetric cross-couplings involved a radical pathway. Generation of LFe–X is followed by halide abstraction from the α-bromo carbonyl compound, resulting in oxidation of the Fe to Fe(II) and generation of the achiral α-carbonyl radical. Transmetallation from the 4-coordinate boron with the resulting Fe(II) forms the Fe–Ar bond. Oxidative capture of the α-carbonyl radical gives the Fe(III) intermediate that can undergo reductive elimination and close the catalytic cycle.



Scheme 4. Iron-catalyzed asymmetric cross-couplings to form profens.

3.3. Cobalt-catalyzed asymmetric cross-couplings for profen derivatives

In 2014, Bian, Zhong and their coworkers[85] reported the first cobalt-catalyzed enantioselective cross-coupling reaction between aryl Grignard reagents and α-bromoesters (Scheme 5). A benzyl-substituted bisoxazoline ligand (BiOX-1) was used and showed excellent enantioselectivity (up to 97%) in the Kumada coupling. Profen derivatives like (*S*)-fenoprofen ester and (*S*)-naproxen ester were generated in 87% yield with 93% *ee* and 57% yield with 90% *ee*, respectively. The reaction was conducted on gram-scale, although the conditions were somewhat limiting (–80 ºC). Subsequently, they found another bisoxazoline ligand (BiOX-2) that showed similar enantioselectivity and efficiency in this Kumada reaction[86]. Highly enantioenriched (*S*)-ibuprofen (64% yield, 98% *ee*) was achieved after lithium hydroxide promoted hydrolysis in 87% yield without racemization. Recrystallized from n-hexane/dichloromethane (20:1) improved the enantiomeric purity from 82% to 98%. More recently, this team reported the first cobalt-catalyzed enantioselective Negishi cross-coupling reaction between arylzinc halides and α-bromoesters[87]. Employing enantioenriched bisoxazoline ligand (BiOX-3), various α-arylalkanoic esters were synthesized in excellent enantioselectivities and yields (up to 97% *ee* and 98% yield), including (*S*)-ibuprofen ester (90% yield with 93% *ee*) and (*S*)-naproxen ester (83% yield with 89% *ee*). Although there have been many Co-catalyzed cross-coupling reactions, mechanistic information remains limited. Similar to the iron-catalyzed process in Scheme 4, the mechanism of the cobalt-catalyzed asymmetric cross-coupling (Scheme 5) involves the generation of radicals, as judged by radical clock studies. The exact timing of the individual steps, and the nature of the species involved, remains to be determined[88]. Nonetheless, it seems reasonable that Co(I) undergoes either halide abstraction from the substrate or SET followed by binding of the halide. The more electrophilic Co(II) will be more suitable for transmetallation. Oxidative capture of the radical increases the Co oxidation state, setting the stage for the reductive elimination.



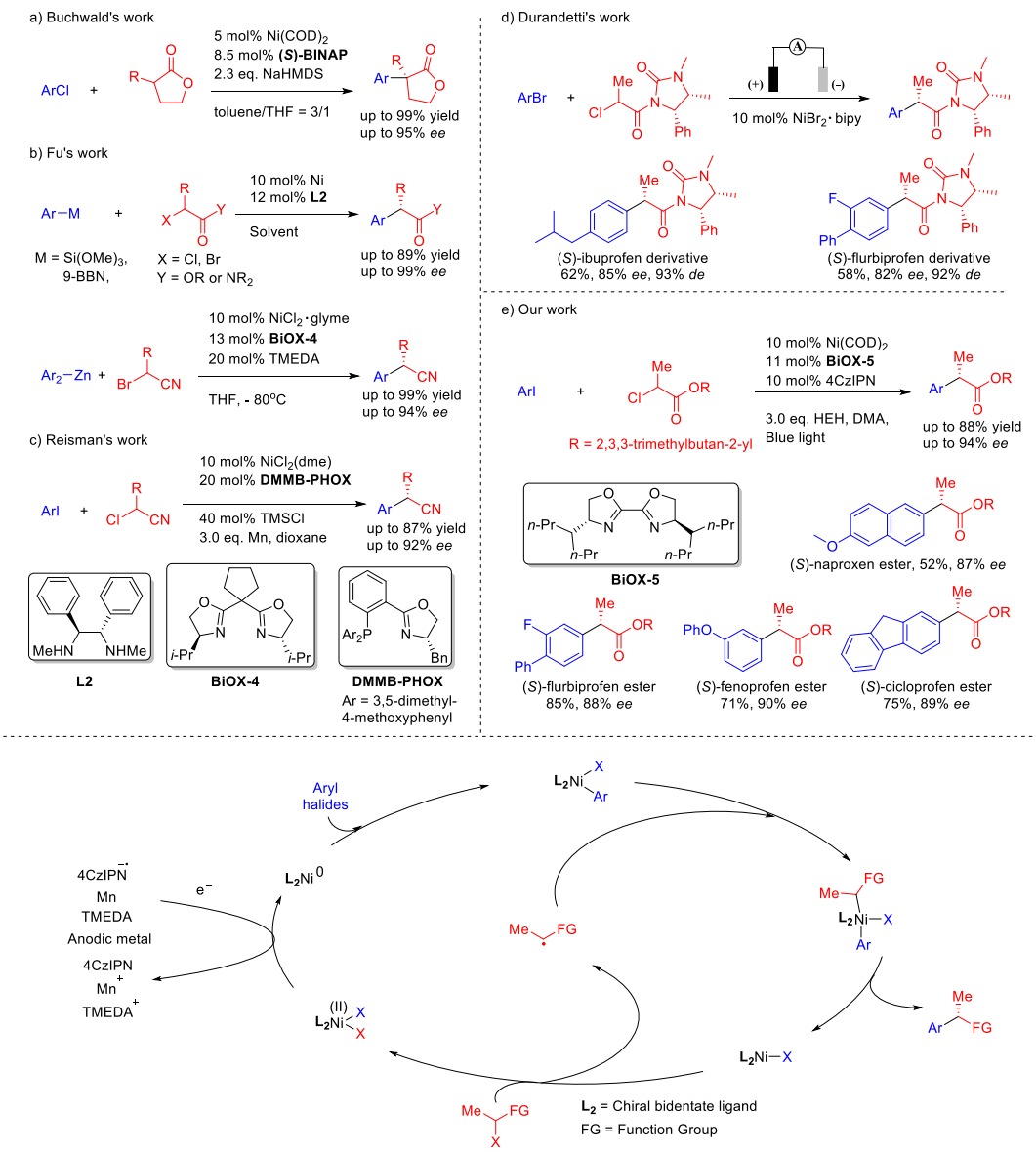
Scheme 5. Cobalt-catalyzed asymmetric cross-couplings toward the synthesis of enantioenriched profens.

3.4. Nickel-catalyzed asymmetric cross-couplings for profen derivatives

Recently, nickel catalysts have attracted much attention because of their low toxicity, unique reactivity and earth abundance[89]. As a result, nickel salts have been explored as catalysts in many types of cross-coupling and related reactions[90-92]. Outlined here are the most relevant reports related to profin derivatives. In 2002, Buchwald and co-workers[93] discovered a Ni-catalyzed enantioselective α-arylation of α-substituted γ-butyrolactones with aryl chlorides (Scheme 6a). In this chemistry, (*S*)-BINAP was paired with the precatalyst $Ni(COD)_2$ (5 mol%) and the resulting catalyst exhibited high efficiency (up to 99% yield) and enantioselectivity (up to 95% *ee*). One downside to this catalyst system, and many examples using $Ni(COD)_2$ is the expense of this air-sensitive precursor, compared to NiX_2-based precursors. The use of the moderately strong base $NaN(SiMe_3)_2$ to deprotonate the pro-nucleophile restricted the substrates to those that would undergo the arylation to generate a chiral quaternary center. Using this approach, it would be difficult to construct enantioenriched tertiary α-carbonyl stereocenters, because the α-hydrogens are more acidic by about 5 pK units compared to the starting carbonyl compounds. Such a process leads to the formation of the achiral enolate, which may also result in undesired double arylation[77].

To avoid the product deprotonation/racemization issue, a series of Ni-catalyzed asymmetric cross-coupling reactions between aryl metal reagents and racemic α-halo compounds were developed. This approach was primarily developed by Fu and co-workers[94-104]. In 2008, they reported the first example of Ni-catalyzed asymmetric cross-coupling between α-halo carbonyl compounds and organosilicon reagents[105]. Diamine ligand (**L2**) was the most appropriate enantioenriched ligand, affording the cross-coupled products in excellent yields (up to 89%) and enantioselectivities (up to 99%). Two years later, they employed the same ligand (**L2**) to achieve the enantioselective Suzuki arylation of racemic α-chloroamides with boron species[106]. In 2012, Fu and co-workers developed the first stereoconvergent cross-coupling of racemic α-halonitriles[107]. Bisoxazoline ligand (BiOX-4) was successfully employed in this asymmetric Negishi arylation, giving the corresponding products in up to 99% yield with up to 94% *ee* (Scheme 6b). Although there were no examples of profen derivatives, these works paved the way for the synthesis of enantioenriched profens using Fu's approach.

An impactful trend in transition metal-catalyzed coupling reactions that influenced the synthesis of profens is cross-electrophile coupling reactions[108]. Such processes paired two electrophiles with a reducing metal[109-111] or organic reductant[112-119]. In 2015, Reisman and co-workers[116] employed the cross-electrophile coupling approach and reported a Ni-catalyzed asymmetric reductive coupling of heteroaryl iodides and α-chloronitriles. The corresponding products were related to profen derivatives, as shown in Scheme 6c. In this pioneering work, the Reisman team used manganese powder (Mn) as a stoichiometric reductant to supply the needed electrons for the cross-electrophile coupling and turn over the Ni catalyst. The enantioenriched ligand (DMMB-PHOX) was employed with readily available $(DME)NiCl_2$ (10 mol%) and exhibited up to 87% yield with excellent enantioselectivity (up to 92% *ee*). Additionally, this reductive cross-coupling reaction avoided the use of reactive and air-sensitive organometallic coupling partners that can limit the functional group tolerance of standard cross-couplings. The downside of the cross-electrophile coupling reaction is they usually utilize metal-reducing agents and generate stoichiometric metal waste[120]. A related strategy is to employ an environmentally friendly reductant to replace metal-reducing agents. Using anodic metal as reductants, Durandetti and co-workers[121] reported a nickel-catalyzed enantioselective electroreductive cross-coupling between α-chloropropionic acid derivatives and aryl bromides (Scheme 6d). An enantioenriched imide acted as an auxiliary to control the stereochemical induction. Enantioenriched profen derivatives of (*S*)-ibuprofen (62% yield, 85% *ee*, 93% de) and (*S*)-flurbiprofen (58% yield, 82% *ee*, 92% de) were successfully afforded. In 2020, we reported the first example of nickel/organic photoredox co-catalyzed asymmetric reductive cross-coupling,[122] which was applied to the synthesis of (*S*)-proxens, such as (*S*)-naproxen, (*S*)-flurbiprofen, (*S*)-fenoprofen and (*S*)-cicloprofen (Scheme 6e). Key features and advantages of this method include broad scope with high enantioselectivities (up to 94%) and good yields (up to 88%) and the avoidance of organometallic coupling partners and stoichiometric metal reductants. The combination of organic reductants Hantzsch ester (HEH)[123, 124] and Cy_2NMe[109, 125, 126] are necessary for the excellent reactivity. Both the chiral bioxazoline ligand (BiOX-5) and the steric hindrance of the ester group were found to play an important role in the enantioselectivity. Mechanistic studies indicate that this asymmetric reductive cross-coupling process likely involves a radical pathway and Ni oxidation states from 0 to III. The enantioenriched L_2Ni^0 oxidatively adds the aryl halide to give $L_2Ni(Ar)X$. Meanwhile, a Ni(I) intermediate undergoes SET with the alkyl halide, generating an α-carbonyl radical. Oxidative capture of this radical by $L_2Ni(Ar)X$ generates a Ni(III) intermediate that undergoes reductive elimination to afford L_2NiX, the species that reduces the alkyl halide. The cycle is closed by the reduction of the resulting Ni(II) to Ni(0) by one of the reducing methods in Scheme 6.

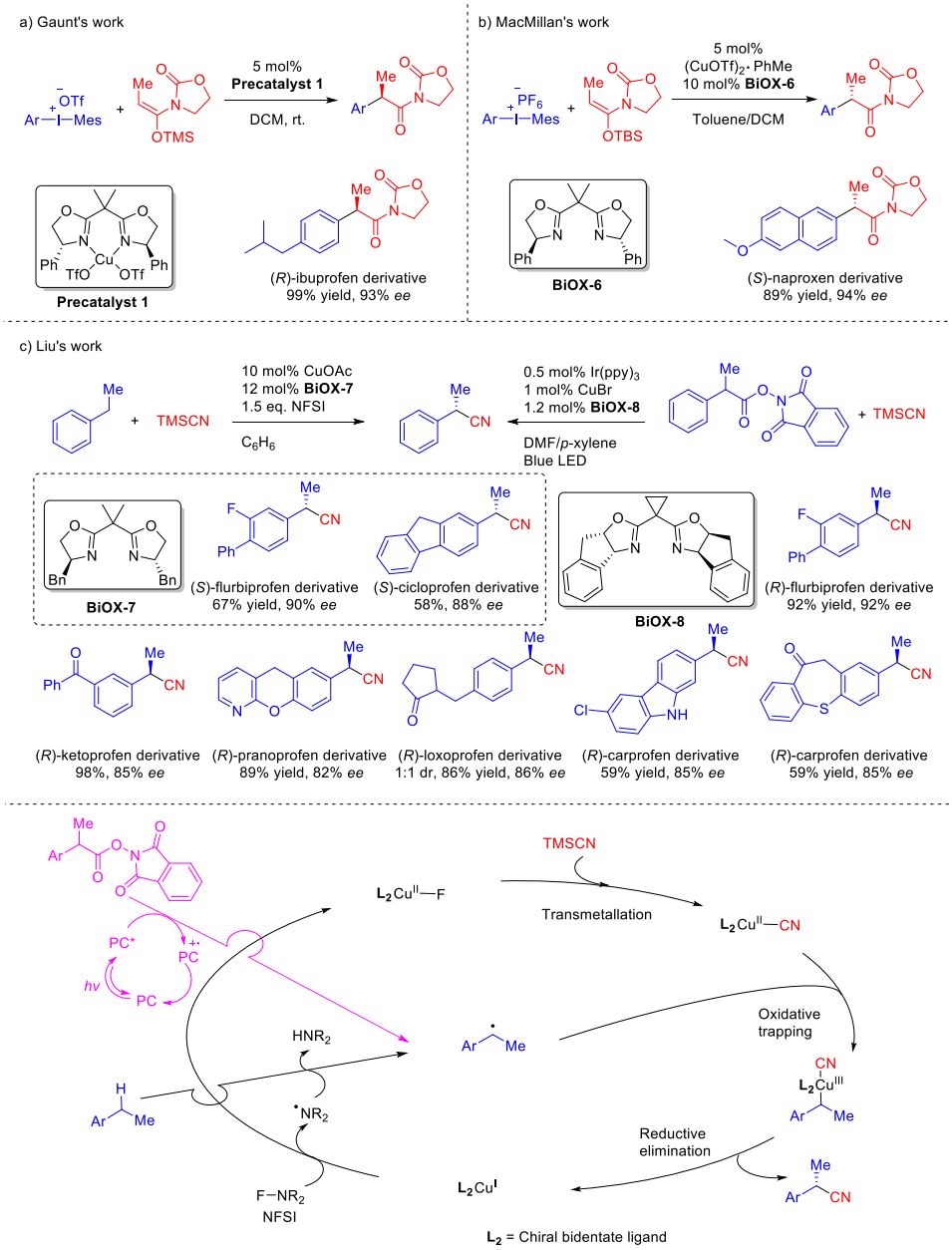


Scheme 6. Nickel-catalyzed asymmetric cross-electrophile couplings toward enantioenriched profens.

3.5. Copper-catalyzed asymmetric cross-couplings on the way to profen derivatives

The use of copper catalysts is also attractive because of the abundance of copper in the Earth's crust. In 2011, Gaunt and co-workers[127] developed a copper(II)-catalyzed asymmetric *α*-arylation of *N*-acyloxazolidinones with diaryliodonium salts. An enantioenriched catalyst precursor (Precatalyst 1), generated from $Cu(OTf)_2$ and (*R*,*R*)-diphenyl-bisoxazoline, showed excellent efficiency (up to 99% yield) and enantioselectivities (up to 95% *ee*) (Scheme 7a). Although the mechanism of this reaction is not clear, the operationally simple protocol provides a new approach to the synthesis of enantioenriched profen derivatives. (*R*)-Ibuprofen derivatives were prepared in 99% yield and 93% *ee* in DCM at room temperature. Almost at the same time, MacMillan and co-workers[128] reported a similar example of an enantioselective *α*-arylation of *N*-acyloxazolidinones with diaryliodonium salts *via* copper-bisoxazoline catalyst (Scheme 7b). (*S*,*S*)-Diphenyl-bisoxazoline (BiOX-6) was employed and the resulting catalyst exhibited excellent efficiency (up to 96% yield) and enantioselectivities (up to 95% *ee*). The (*S*)-naproxen derivative formed in 89% yield with 94% *ee via* this transformation in a mixed medium (DCM/toluene) at 0 °C. In 2016, Liu and Stahl[129] reported a copper-catalyzed enantioselective conversion of benzylic C–H bonds into benzylic nitriles, which are precursors to profens (Scheme 7c, left). In this work, (*S*,*S*)-dibenzyl bisoxazoline (BiOX-7) showed excellent efficiency (up to 91% yield) and enantioselectivities (up to 98% *ee*). Radical-probe experiments indicated that this copper-catalyzed asymmetric transformation likely involves a radical relay pathway. One year later, Liu and Lin[130] reported a related example of copper/photoredox-catalyzed enantioselective decarboxylative cyanation of *N*-hydroxy-phthalimide (NHP) esters (Scheme 7c, right). Similar to their previous work, a chiral ligand-bearing bisoxazoline (BiOX) framework was the most promising. In this case, BiOX-8 was the best in this reaction among the ligands examined, giving the corresponding profen precursors in moderate to excellent yields (59–98%) and good to excellent ee (85–96%). A series of

racemic arylpropanoic acids such as flurbiprofen, ketoprofen, pranoprofen, loxoprofen, carprofen and zaltoprofen were transformed into the corresponding enantioenriched benzylic nitriles by merging photoredox catalysis with copper catalysis.

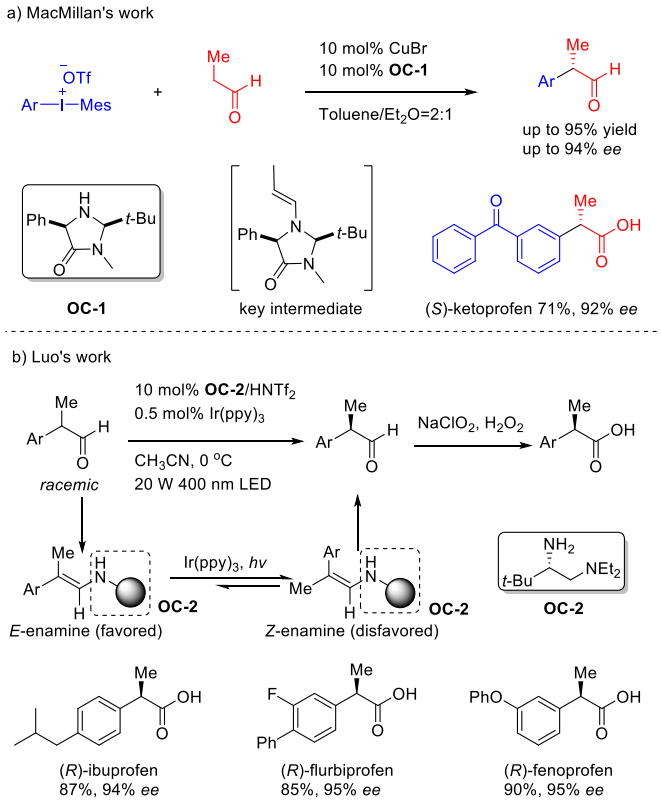


Scheme 7. Copper-catalyzed asymmetric cross-couplings for the synthesis of profens.

4. Organocatalysis approaches to profens

The stereocontrolled formation of C–C bonds through asymmetric organocatalysis is a promising, yet challenging approach. The pioneering works of MacMillan,[131, 132] Barbas,[133] and List[134, 135] added a new pillar to the field of asymmetric catalysis, which had been dominated by enzymes and transition metal catalysts. Over the last few years, the development of novel small organic molecule-based catalysts for organic transformations has increased noticeably, including providing an alternative strategy for the synthesis of profen derivatives. In 2011, MacMillan and co-workers[136] reported enantioselective α-arylation of aldehydes with diphenyliodonium triflates *via* a combination of copper and organic catalysts (Scheme 8a). The imidazolidinone catalyst (OC-1) forms a key covalent enamine intermediate that affects the activation of the aldehyde and the creation of the new stereocenter. After oxidation of the aldehyde to the acid, (*S*)-ketoprofen was furnished in 71% overall yield and 92% *ee*. In 2022, Luo[137] combined simple aminocatalysis (OC-2) with readily available photosensitizers to successfully achieve deracemization of α-branched aldehydes (Scheme 8b). Catalytic deracemization of α-branched aldehydes was a direct strategy to construct enantiopure α-tertiary carbonyls, which were direct precursors to optical enantioenriched profens. Mechanistic studies indicated that photochemically *E*/*Z* isomerization and the stereospecificity of enamine protonation by OC-2 were the two key steps in the deracemization of α-branched aldehydes. (*R*)-Ibuprofen (87%, 94% *ee*), (*R*)-flurbiprofen (85%, 95% *ee*) and (*R*)-fenoprofen (90%, 95% *ee*) could be easily obtained *via* a

simple oxidation from their corresponding enantioenriched aldehydes.



Scheme 8. Organocatalytic asymmetric synthesis for profens.

5. Conclusions and outlook

The profen family of molecules is among the most commonly used medications in the world, resulting in billions in annual sales[138]. Motivated by their remarkable activity and utility, great strides have been made toward their synthesis using asymmetric catalysis. Nonetheless, there is still room for improvement on issues such as catalyst cost, catalyst toxicity, ligand availability and stability and green chemistry[139]. With regard to the asymmetric TM-catalyzed approaches, new methods employing first-row transition-metal catalysts have recently emerged and are opening new perspectives in the synthesis of highly enantioenriched profens. Combined with their Earth abundance and low toxicity, the use of these metals is expected to become a viable substitute for expensive transition-metals (such as Ru, Ir, Pd). It is also anticipated that more convergent approaches, like those involving enantioselective C–C bond formation, will continue to gain traction relative to enantioselective hydrogenations.

Asymmetric organocatalysis is an area of much current interest. It has several attractive features, such as transition metal-free processes, mild reaction conditions and new modes of activation. These organocatalysts better satisfy the principles of green chemistry and sustainability. Although remarkable progress has been achieved in asymmetric organocatalytic synthesis of enantioenriched profens, the potential of this strategy has not been fully achieved. Further developments with novel organocatalyst systems that require lower catalyst loadings are in demand and anticipated to be important grounds for future development toward the synthesis of profens and their derivatives.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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