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# Recent developments in enantioselective nickel(II)-catalyzed conjugate additions

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**Abstract:** This review highlights the recent developments in enantioselective nickel-catalyzed conjugate additions of various nucleophiles to numerous acceptor-activated olefins published since 2016. By the very fact of the lower costs of nickel catalysts in comparison with other transition metals, these reactions represent powerful and economic methodologies for the stereocontrolled formation of carbon-carbon and carbon-heteroatom bonds. When applied to initiate domino reactions, these processes allowed a direct access to a variety of complex and functionalized chiral molecules.

## 1. Introduction

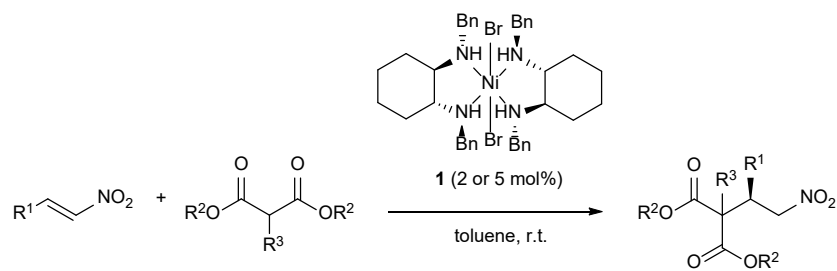
By the very fact of the lower costs of nickel catalysts in comparison with other transition metals,<sup>1</sup> enantioselective nickel-catalyzed reactions of many types have received a continuous ever-growing attention in the last decade.<sup>2,3,4,5</sup> This interest might also be related to the fact that nickel complexes are of high abundance, and exhibit a remarkably diverse chemical reactivity. Nickel has a small atomic radius, and Ni-ligand bond lengths are often relatively short, producing solid and dense complexes. Indeed, several key properties of nickel, such as easy access to multiple oxidation states, facile oxidative addition, and facile activation have allowed the development of a broad range of unprecedented and challenging transformations. This usefulness is particularly highlighted in the area of enantioselective conjugate additions of nucleophiles to acceptor-activated carbon-carbon double bonds. The first metal-catalyzed Michael addition<sup>6</sup> was reported in 1972 by Saegusa et al., dealing with a copper-mediated addition of malonates and diketones to  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>7</sup> Later in 1979, Nelson et al. employed for the first time nickel as metal to promote this type of reactions,<sup>8</sup> which made nickel becoming one of the preferred metals used in catalytic Michael reactions.<sup>9</sup> In 1988, Soai et al. disclosed the first enantioselective nickel-catalyzed conjugate addition which provided a moderate enantioselectivity (55% ee),<sup>10</sup> albeit improved up to 90% ee soon later in 1989.<sup>11</sup> Ever since, a wide variety of chiral nickel catalysts have been successfully applied to catalyze many types of highly enantioselective conjugate additions among which a number belonging to asymmetric domino reactions. The goal of this review is to cover the advances in enantioselective nickel-catalyzed conjugate additions reported since the beginning of 2016 since this special field was most recently reviewed in 2015.<sup>12</sup> It must be noted that more general asymmetric metal-catalyzed conjugate additions were reviewed in 2018 by Feng et al.,<sup>13</sup> and by Reznikov and Klimochkin in 2020.<sup>14</sup> However, the former review from 2018 included only three references  $\geq 2016$  dealing with nickel catalysis, and the second review from 2020 collected only one reference  $\geq 2016$  focussing on nickel-catalyzed Michael reactions. Moreover, Xu et al. reviewed in 2017 the field of metal-catalyzed asymmetric Michael addition in natural product synthesis albeit including none reference  $\geq 2016$  about nickel-catalyzed reactions.<sup>15</sup> The present review is divided into three parts, dealing successively with enantioselective nickel-catalyzed conjugate additions to nitroalkenes, enantioselective nickel-catalyzed conjugate additions to  $\alpha,\beta$ -unsaturated carbonyl compounds and derivatives, and enantioselective nickel-catalyzed domino and tandem processes based on a Michael addition. The first part is subdivided into two sections, according to the different types of nucleophiles to be added to nitroalkenes, e.g. 1,3-dicarbonyl compounds and derivatives and other nucleophiles. The second part is also subdivided into two sections, dealing successively with additions of carbon nucleophiles and other nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds and derivatives.

## 2. Conjugate additions to nitroalkenes

### 2.1. 1,3-Dicarbonyl compounds and derivatives as nucleophiles

#### 2.1.1. Homogeneous catalysts

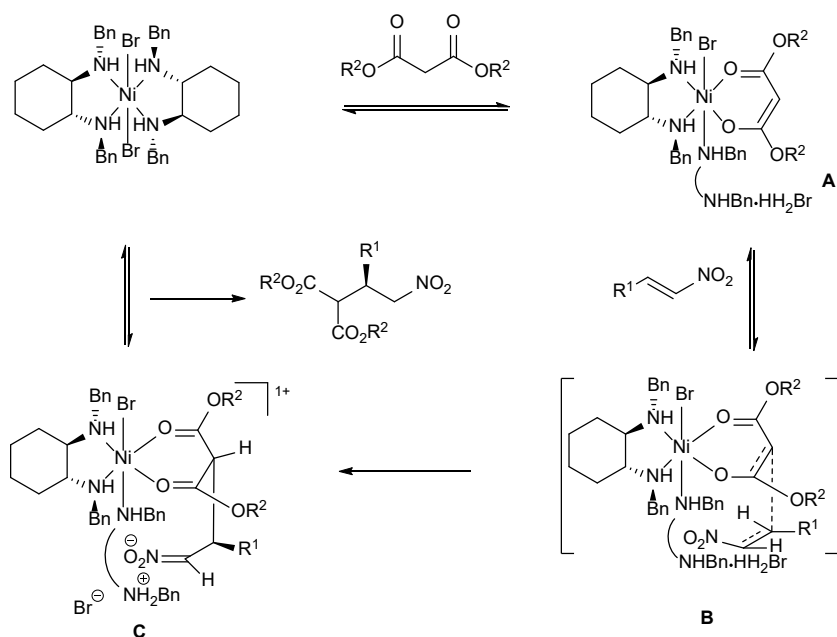
Enantioselective additions of nucleophiles to nitroalkenes resulted in the formation of functionalized chiral products,<sup>6f,16</sup> which represent key molecules in synthesis related to the nitro group opening the route to diverse subsequent transformations.<sup>17</sup> Among carbon nucleophiles, the most employed in asymmetric conjugate additions are 1,3-dicarbonyl compounds, such as malonates, related to the fact that the two carbonyl groups can chelate with a metal center to form a stable six-membered structure. One of the most important advances in the area of enantioselective nickel-catalyzed Michael additions of nucleophiles to nitroalkenes was disclosed by Evans and Seidel, in 2005.<sup>18</sup> Although not belonging to the period covered by this review, this key work is remembered in Scheme 1 related to its importance. It dealt with asymmetric conjugate additions of 1,3-dicarbonyl compounds to nitroalkenes, leading to the corresponding products with enantioselectivities of up to 97% ee by using a novel readily available chiral nickel(II) catalyst **1** based on a *trans*-1,2-diaminocyclohexane chiral ligand. The catalyst was sufficiently basic to promote the enolization of the 1,3-dicarbonyl compound, alleviating the need for the addition of an ancillary base. Subsequently, one diamine ligand was partially released as its conjugate acid, resulting in the formation of enolate **A**. Then, nucleophilic attack of intermediate **A** on the nitroalkene proceeded through plausible transition structure **B**, where reinforcing steric and electrostatic effects could orient the nitroalkene moiety. Intramolecular proton transfer from the pendant ammonium ion to the nitronate anion in intermediate **C** and subsequent product dissociation completed the catalytic cycle. Therefore, the two amine ligands in the catalyst system each played a distinct role: one served as a chiral ligand to provide stereoselectivity in the addition step while the other functioned as a base for substrate enolization.



82-99%, 88-97% ee

- R<sup>1</sup> = Ph, R<sub>2</sub> = Me, R<sub>3</sub> = H: 99%, 94% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = Et, R<sub>3</sub> = H: 99%, 95% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = *i*-Pr, R<sub>3</sub> = H: 96%, 95% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = *t*-Bu, R<sub>3</sub> = H: 97%, 95% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = Bn, R<sub>3</sub> = H: 99%, 95% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = R<sub>3</sub> = Me: 95%, 95% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = Et, R<sub>3</sub> = NHAc: 92%, 94% ee
- R<sup>1</sup> = *p*-Tol, R<sub>2</sub> = Et, R<sub>3</sub> = H: 99%, 95% ee
- R<sup>1</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = Et, R<sub>3</sub> = H: 99%, 95% ee
- R<sup>1</sup> = *p*-BrC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = Et, R<sub>3</sub> = H: 99%, 95% ee
- R<sup>1</sup> = *o*-ClC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = Et, R<sub>3</sub> = H: 98%, 92% ee
- R<sup>1</sup> = 2,3-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R<sub>2</sub> = Et, R<sub>3</sub> = H: 99%, 93% ee
- R<sup>1</sup> = 2,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R<sub>2</sub> = Et, R<sub>3</sub> = H: 98%, 94% ee
- R<sup>1</sup> = 3,4-(OCH<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R<sub>2</sub> = Et, R<sub>3</sub> = H: 97%, 95% ee
- R<sup>1</sup> = 2-furyl, R<sub>2</sub> = Et, R<sub>3</sub> = H: 98%, 95% ee
- R<sup>1</sup> = *n*-Pent, R<sub>2</sub> = Et, R<sub>3</sub> = H: 98%, 95% ee
- R<sup>1</sup> = *i*-Bu, R<sub>2</sub> = Et, R<sub>3</sub> = H: 94%, 88% ee
- R<sup>1</sup> = *i*-Pr, R<sub>2</sub> = Et, R<sub>3</sub> = H: 82%, 90% ee

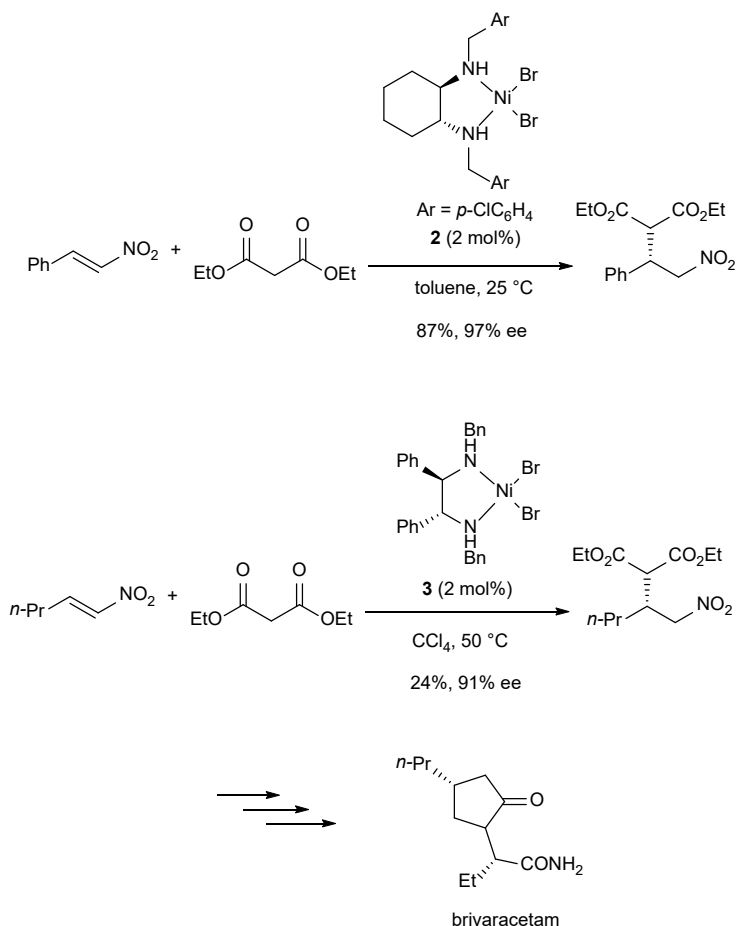
proposed mechanism:



**Scheme 1** Early conjugate addition of malonates to nitroalkenes reported by Evans.

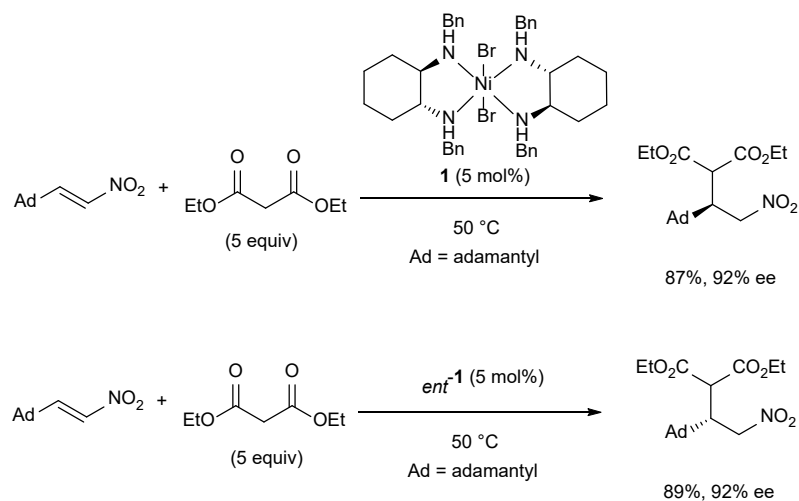
In 2018, Reznikov et al. reported the synthesis of novel nickel complexes bearing chiral ligands derived from chiral 1,2-diamines.<sup>19</sup> Their catalytic activity in the enantioselective Michael addition of diethyl malonate to  $\beta$ -phenyl nitroalkene was investigated. When using only 2 mol% of catalyst **2** in toluene at 25 °C, diethyl malonate added to  $\beta$ -phenyl nitroalkene to

give the corresponding chiral product in 87% yield and 97% ee (Scheme 2). A slightly higher enantioselectivity (97% ee vs 95%) in comparison with the original Evans's methodology was probably due to the presence of bulkier substituents (Ar = *p*-ClC<sub>6</sub>H<sub>4</sub> instead of Ph) at the nitrogen atoms of the chiral ligand. In the reaction of an alkyl-substituted nitroalkene, such as 1-nitropent-1-ene, with the same malonate, the optimal catalyst was found to be **3** employed at 50 °C at the same catalyst loading in CCl<sub>4</sub> as the solvent, allowing the synthesis of the desired chiral product to be achieved in low yield (24%) albeit combined with a high enantioselectivity (91% ee). The latter constituted the key intermediate in a total synthesis of antiepileptic drug brivaracetam.

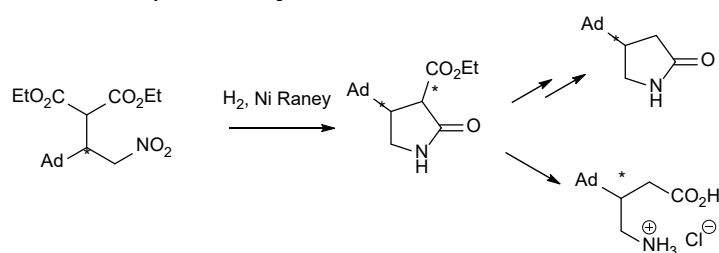


**Scheme 2** Michael additions of diethyl malonate to phenyl- and propyl-substituted nitroalkenes in the presence of nickel complexes bearing chiral ligands derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamines.

$\gamma$ -Amino acids and their cyclic derivatives (pyrrolidin-2-ones) are known to affect the central nervous system.<sup>20</sup> The adamantane fragment constitutes a privileged framework found in the structure of many drugs, since it increases their bioavailability. In this context, Sibiryakova et al. developed in 2019 the synthesis of novel adamantylated chiral GABA derivatives on the basis of enantioselective Michael addition of diethyl malonate to 1-(adamant-1-yl)-2-nitroethene.<sup>21</sup> The reaction employed 5 mol% of preformed chiral nickel catalyst **1** at 50 °C. No solvent was needed but an excess of diethyl malonate was used (5 equivalents). When catalyzed by this complex, the reaction afforded the chiral Michael product with 87% yield and 92% ee while employing *ent*-**1** as catalyst resulted in the formation of the enantiomeric product with 89% yield and 92% ee (Scheme 3). Each of these products were converted into desired novel adamantylated GABA derivatives, such as (*R*)- and (*S*)-4-(1-adamantyl)pyrrolidin-2-ones and (*R*)- and (*S*)-4-aminobutyric acids. It must be noted that this work constituted the first use of bulky adamantane-containing nitroalkenes in enantioselective nickel-catalyzed Michael additions and presented the advantage in comparison with Evans's methodology to need no solvent.

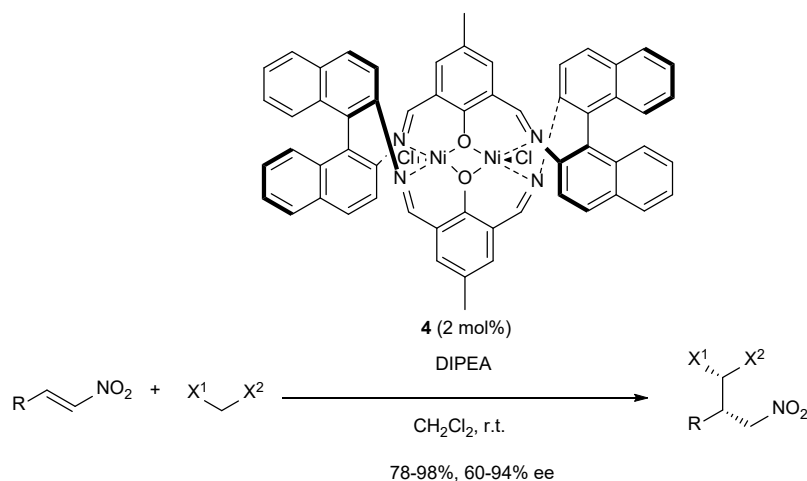


Synthesis of adamantyl GABA analogues:



**Scheme 3** Michael additions of diethyl malonate to 1-(adamant-1-yl)-2-nitroethene and synthesis of adamantylated GABA derivatives.

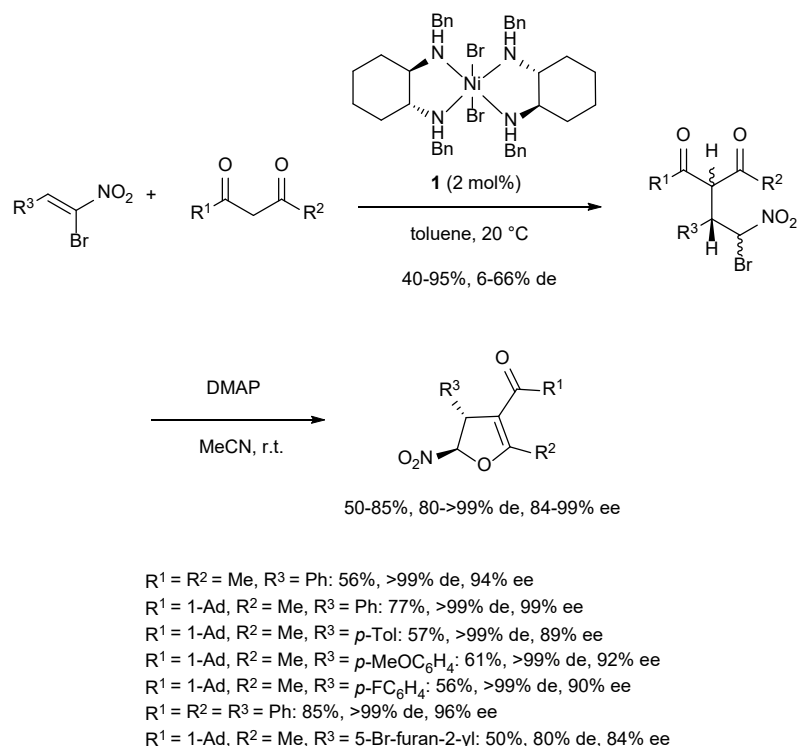
Later in 2020, Subramanian et al. described the synthesis of novel binuclear nickel(II) helicates through self-assembly of chiral 1,1'-binaphthyl-2,2'-diamine, 4-methyl-2,6-diformyl phenol and nickel salts.<sup>22</sup> These dinuclear double stranded Ni(II) helicates were characterized by crystal X-ray diffraction and further investigated as catalysts in asymmetric Michael additions of various 1,3-dicarbonyl compounds and derivatives to nitroalkenes. The optimal catalyst was found to be complex **4** employed at room temperature at 2 mol% of catalyst loading in dichloromethane as solvent. Performed in the presence of DIPEA as base, the formation of chiral Michael products was achieved in uniformly high yields (78-98%) and moderate to excellent enantioselectivities (60-94% ee), as illustrated in Scheme 4. Different types of Michael donors were tolerated, spanning from malonates, malononitrile, malonyl chloride, ethyl cyanoacetate, ethyl bromoacetate, methyl and ethyl 2-pyridylacetates to barbituric acid and dimedone, which all produced the desired products with both high yields and enantioselectivities. Moreover, the catalyst system was compatible with differently substituted  $\beta$ -nitroalkenes. In addition to (hetero)aryl-substituted nitroalkenes which reacted with good to high ee values (72-94% ee), alkyl-substituted nitroalkenes ( $R = n\text{-Pr}, n\text{-Pent}$ ) were also compatible, albeit leading to the corresponding products with lower ee values (60-66% ee). The authors suggested that this result indicated a possible strong  $\pi$ - $\pi$  interaction between aromatic nitrostyrenes and the catalyst. In comparison with Evans's methodology, this novel method presented the advantage to use a recyclable catalyst for up to nine times without any significant loss in enantioselectivity and yield. Even if the observed enantioselectivities were generally slightly lower, the scope was broad especially for the Michael donors.



R = Ph, X<sup>1</sup> = X<sup>2</sup> = COEt: 98%, 90% ee  
 R = Ph, X<sup>1</sup> = X<sup>2</sup> = COCl: 96%, 89% ee  
 R = Ph, X<sup>1</sup> = X<sup>2</sup> = CN: 98%, 78% ee  
 R = Ph, X<sup>1</sup> = CN, X<sup>2</sup> = COEt: 90%, 80% ee  
 R = Ph, X<sup>1</sup> = Br, X<sup>2</sup> = COEt: 92%, 78% ee  
 R = Ph, X<sup>1</sup> = 2-pyridyl, X<sup>2</sup> = CO<sub>2</sub>Me: 88%, 76% ee  
 R = Ph, X<sup>1</sup> = 2-pyridyl, X<sup>2</sup> = CO<sub>2</sub>Et: 86%, 74% ee  
 R = Ph, X<sup>1</sup>, X<sup>2</sup> = OCNHCONHCO: 78%, 72% ee  
 R = Ph, X<sup>1</sup>, X<sup>2</sup> = OCCH  
 R = Ph, X<sup>1</sup>, X<sup>2</sup> = C(Me)<sub>2</sub>CH<sub>2</sub>CO: 90%, 86% ee  
 R = *p*-FC<sub>6</sub>H<sub>4</sub>, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 98%, 94% ee  
 R = *p*-ClC<sub>6</sub>H<sub>4</sub>, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 95%, 92% ee  
 R = *p*-BrC<sub>6</sub>H<sub>4</sub>, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 90%, 90% ee  
 R = *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 92%, 86% ee  
 R = *p*-MeOC<sub>6</sub>H<sub>4</sub>, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 88%, 80% ee  
 R = 9-anthrenyl, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 92%, 88% ee  
 R = 2-pyridyl, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 93%, 85% ee  
 R = *n*-Pr, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 82%, 66% ee  
 R = *n*-Pent, X<sup>1</sup> = X<sup>2</sup> = CO<sub>2</sub>Et: 80%, 60% ee

**Scheme 4** Michael addition of 1,3-dicarbonyl compounds and derivatives to nitroalkenes in the presence of dinuclear double stranded Ni(II) helicates.

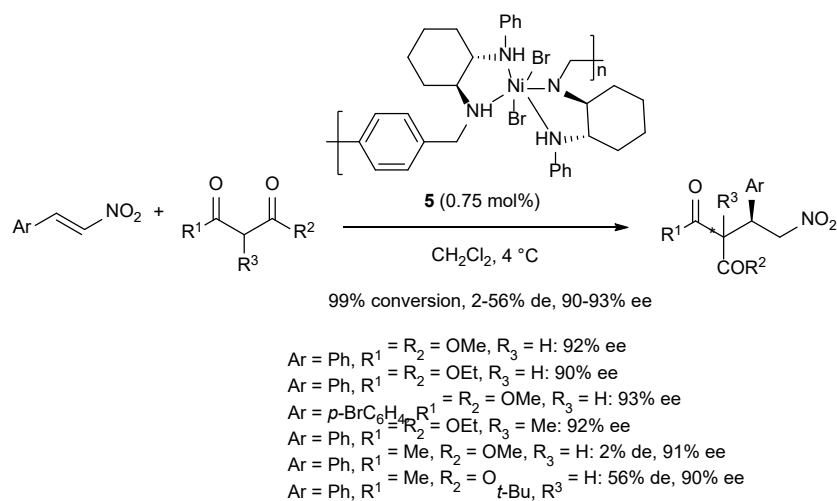
With the aim of developing a simple methodology for the synthesis of chiral *trans*-4,5-dihydrofurans that constitute the key skeletons of numerous bioactive and natural products, Nikerov et al. applied in 2021 2 mol% of chiral nickel catalyst **1** to promote the asymmetric Michael addition of 1,3-diketones to  $\alpha$ -bromonitroolefins.<sup>23</sup> As shown in Scheme 5, the process performed at 20 °C in toluene as solvent afforded the corresponding chiral nitroketones as mixture of diastereomers in moderate to high yields (40-95%) and low to moderate diastereoselectivities (6-66% de). This mixture was subsequently submitted to cyclization by treatment with DMAP in acetonitrile as solvent, resulting in the formation of desired chiral tetrasubstituted 4,5-dihydrofurans obtained with good yields (50-85%), combined with both high *trans*-diastereo- (80->99% de) and enantioselectivities (84-99% ee). This work represented a beautiful extension of the original Evans's methodology, allowing the synthesis of novel chiral adamantyl-substituted dihydrofurans as almost single *trans*-diastereomers (80->99% de) with high enantioselectivities (84-99% ee).



**Scheme 5** Michael addition of 1,3-diketones to  $\alpha$ -bromonitroolefins and synthesis of tetrasubstituted 4,5-dihydrofurans.

### 2.1.2. Heterogeneous catalysts

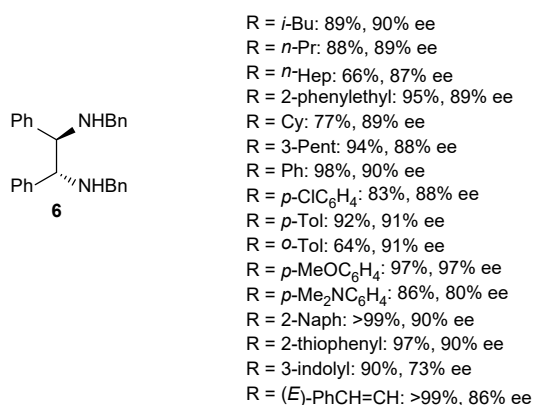
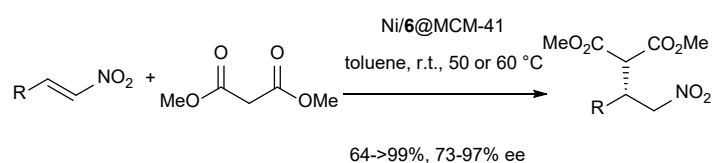
Most chiral homogeneous catalysts are not compatible to valuable scale-up application and, even more importantly, suffer from two main drawbacks which are their inability to be reused and the possible product contamination. In this context, the development of recyclable heterogeneous chiral catalysts are challenging and in accordance with green and more economic catalysis. In 2016, Laponnaz et al. reported the synthesis of novel recyclable, robust and self-supported polymeric nickel catalysts based on chiral cyclohexyl diamine-containing ditopic ligands.<sup>24</sup> These nickel metallopolymers were investigated as promoters in enantioselective Michael additions of 1,3-dicarbonyl compounds to nitrostyrenes. Optimal catalyst **5** derived from  $\text{NiBr}_2$  was employed at 4 °C at a low catalyst loading of 0.75 mol% in dichloromethane as solvent, allowing the synthesis of the chiral Michael products with complete conversion and high enantioselectivities (90-93% ee), as shown in Scheme 6. Furthermore, this air- and moisture-stable catalyst system was found recyclable for up to eleven times without loss of either activity or enantioselectivity which illustrates the strength of this novel methodology.





**Scheme 6** Michael addition of malonates/ $\beta$ -ketoesters to nitrostyrenes in the presence of a self-supported chiral polymeric nickel catalyst.

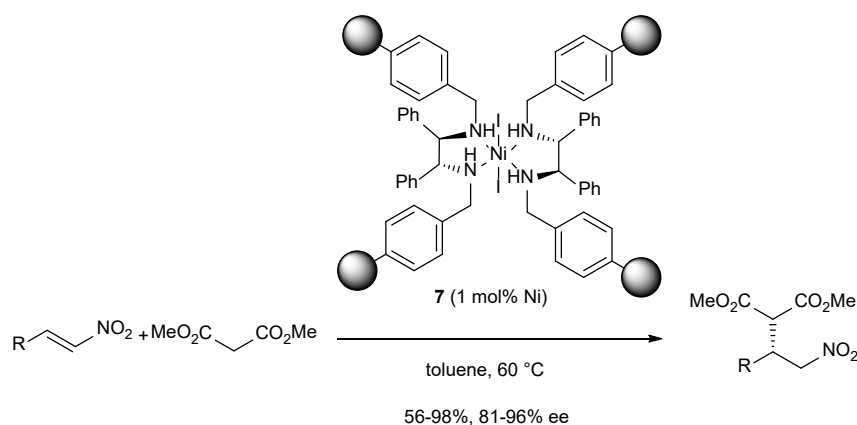
In 2019, Ishitani and Kobayashi demonstrated that chiral diamine nickel complexes of this type could be immobilized on MCM-41, which is a mesoporous material with a hierarchical structure based on silicate and aluminosilicate solids.<sup>25</sup> The immobilization was achieved through the wet impregnation methodology, consisting in introducing the metal precursor dissolved in an organic solvent to the catalyst support through capillary action causing absorption of the solution into the pores. The pure catalyst was obtained after the postcalcination process which eliminated the presence of volatile compounds inside the solution. This novel heterogeneous catalyst was further used as efficient heterogeneous catalysts in comparable asymmetric Michael additions. As shown in Scheme 7, the reaction of dimethyl malonate with nitroalkenes performed in toluene at room temperature, 50 °C or 60 °C in the presence of catalyst Ni/**6**@MCM-41 derived from 2 mol% of chiral 1,2-diphenylethane-1,2-dibenzylamine **6** led to the corresponding chiral products with both moderate to excellent yields (64->99%) and enantioselectivities (73-97% ee). The authors found a superior catalytic activity of this heterogeneous catalyst in comparison with its homogeneous counterpart. Moreover, it could be simply recovered by filtration and reused for up to three times with keeping the same levels of yield and enantioselectivity. Since Michael reactions of nitroalkenes bearing aliphatic substituents are still much less developed than those with aryl-substituted nitroalkenes, this novel methodology filled a gap with enantioselectivities of 86-90% ee.

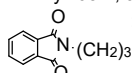


**Scheme 7** Michael addition of dimethyl malonate to nitroalkenes in the presence of an heterogeneous catalyst immobilized on MCM-41.

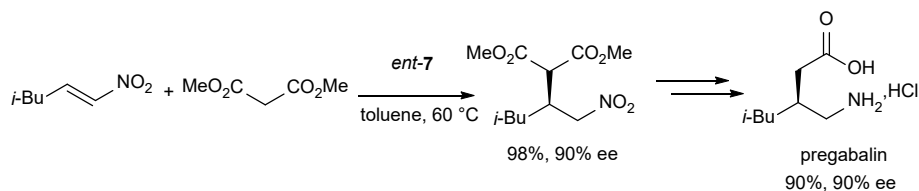
In 2020, Kramer and Kegnaes reported the first incorporation of a chiral nickel(II)-bisdiamine complex in a polystyrene porous organic polymer.<sup>26</sup> This was achieved through copolymerization of vinyl-functionalized nickel(II)-bisdiamine complexes. Novel heterogeneous catalyst **7** was found to be a highly efficient promotor in the asymmetric Michael addition of dimethyl malonate to challenging aliphatic nitroalkenes. The reaction performed at 60 °C in toluene resulted in the formation of the corresponding chiral products with moderate to quantitative yields (56-98%) and uniformly high enantioselectivities (81-96% ee), as presented in Scheme 8. Due to the attachment of the ligands to the support by strong covalent bonds, no ligand leaching took place. To illustrate the generality of the catalyst system, the scope of the methodology was extended to (hetero)aromatic nitroalkenes (R = Ph, 2-thienyl, 2-furyl) which allowed the synthesis of the corresponding products with both high yields (91-98%) and enantioselectivities (96-98% ee). Moreover, the heterogeneous nature of the catalyst made it compatible with continuous flow production. It was recyclable with a turnover number (TON) of 450 after five runs. The synthetic utility of the methodology was demonstrated in a synthesis of the blockbuster drug pregabalin (Scheme 8). By using the enantiomeric catalyst *ent*-**7**, the reaction between dimethyl malonate and *i*-butyl-

substituted nitroalkene led to the corresponding chiral product with 98% yield and 90% ee, which was converted through only two supplementary steps into desired pregabalin with 90% yield and 90% ee. This novel catalyst system presented the advantage to be the first one to allow a good functional group tolerance for the challenging aliphatic nitroalkenes. Indeed, good yields (59-94%) combined with uniformly high enantioselectivities (90-92% ee) were obtained in the reaction of a diversity of aliphatic nitroalkenes bearing sensitive functional groups.



- R = *i*-Bu: 93%, 90% ee
- R = Et: 90%, 90% ee
- R = *n*-Pr: 91%, 90% ee
- R = *n*-Bu: 88%, 93% ee
- R = *i*-Pr: 85%, 90% ee
- R = Cy: 72%, 89% ee
- R = *t*-Bu: 56%, 81% ee
- R = Br(CH<sub>2</sub>)<sub>3</sub>: 66%, 90% ee
- R = Cl(CH<sub>2</sub>)<sub>4</sub>: 88%, 91% ee
- R = PivO(CH<sub>2</sub>)<sub>4</sub>: 64%, 90% ee
- R = BnO(CH<sub>2</sub>)<sub>4</sub>: 94%, 91% ee
- R = MeO(CH<sub>2</sub>)<sub>4</sub>: 83%, 91% ee
- R = TBSO(CH<sub>2</sub>)<sub>4</sub>: 59%, 91% ee
- R = PivNH(CH<sub>2</sub>)<sub>3</sub>: 86%, 92% ee
- R = allylCH<sub>2</sub>: 87%, 90% ee
- R = Ph: 91%, 94% ee
- R = 2-furyl: 96%, 96% ee
- R = 2-thienyl: 98%, 96% ee
- R = : 94%, 92% ee

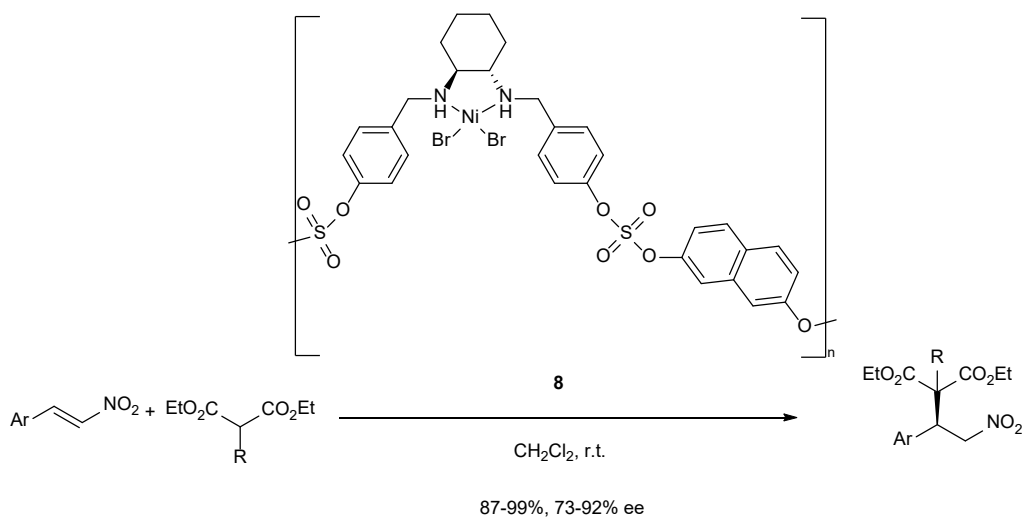
synthesis of pregabalin:



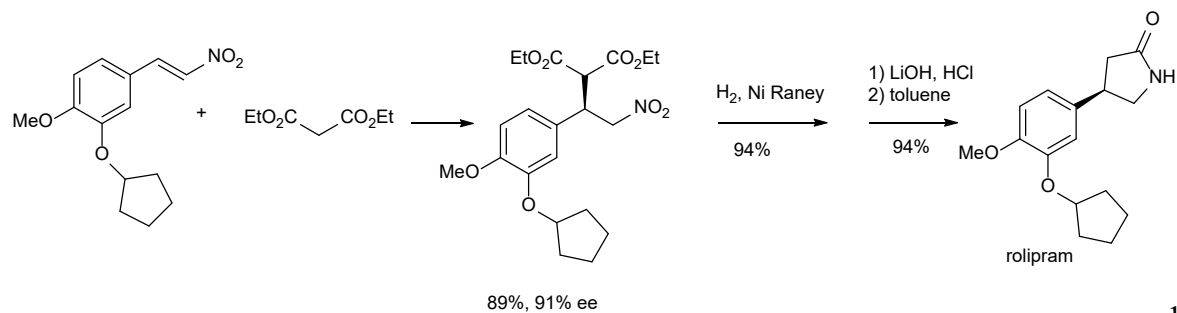
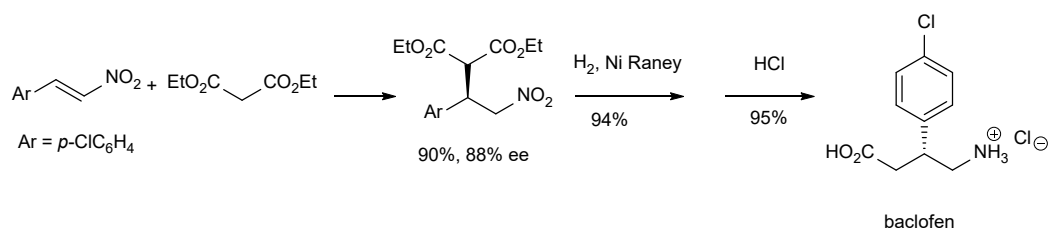
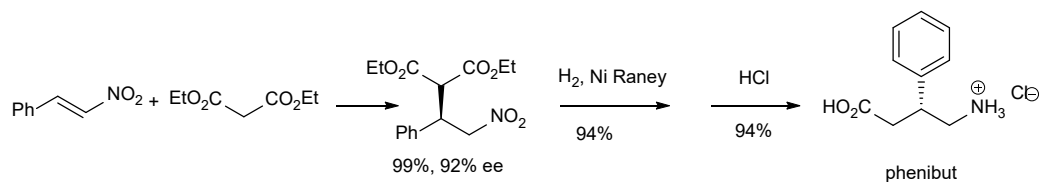
**Scheme 8** Michael addition of dimethylmalonate to nitroalkenes in the presence of a polystyrene-incorporated nickel(II)-bisdiamine complex and synthesis of pregabalin.

In 2021, Zhang and Yan disclosed the first immobilization of a chiral homogeneous catalyst on a polysulfonate chain.<sup>27</sup> It dealt with polysulfonate-supported chiral cyclohexyldiamine-nickel catalyst **8** synthesized through sulfur (VI) fluoride exchange click-reactions. The latter was investigated as promotor in enantioselective Michael addition of diethyl malonates

to  $\beta$ -(hetero)aryl-nitroalkenes performed at room temperature in dichloromethane as solvent (Scheme 9). The formed products were achieved in high yields (87-99%) and moderate to excellent enantioselectivities (73-92% ee). Differently substituted nitroalkenes were compatible with either electron-donating or electron-withdrawing groups on the phenyl ring. A lower enantioselectivity (73% ee) was obtained in the reaction of sterically hindered 2-naphthyl-nitroalkene (Ar = 2-Naph) while better ee values (85-89% ee) were obtained in that of heteroaromatic nitroalkenes (Ar = 2-furyl, 2-indoyl). Furthermore, along with diethyl malonate (R = H), diethyl 2-methylmalonate (R = Me) provided by reaction with  $\beta$ -phenyl nitroalkene (Ar = Ph) the corresponding product with a good enantioselectivity (87% ee) albeit combined with a reduced yield (79%). Notably, the catalyst could be recycled for ten times without loss of activity and enantioselectivity. The methodology was successfully applied to the synthesis of three  $\gamma$ -aminobutyric acid drugs, such as phenibut, baclofen and rolipram. In spite of its remarkable recyclability and efficiency, this novel catalyst system presented the drawback to be incompatible to aliphatic nitroalkenes.



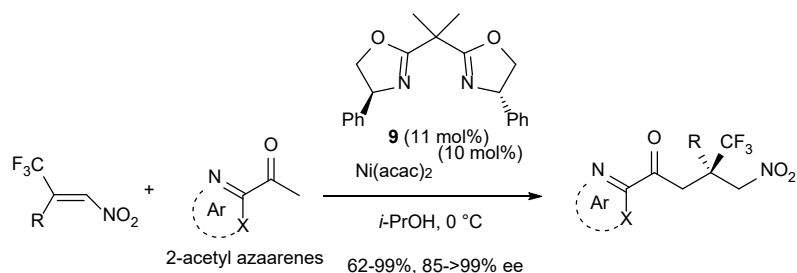
- Ar = Ph, R = H: 99%, 92% ee  
 Ar = *p*-FC<sub>6</sub>H<sub>4</sub>, R = H: 96%, 91% ee  
 Ar = *p*-ClC<sub>6</sub>H<sub>4</sub>, R = H: 90%, 88% ee  
 Ar = *m*-ClC<sub>6</sub>H<sub>4</sub>, R = H: 95%, 89% ee  
 Ar = *o*-ClC<sub>6</sub>H<sub>4</sub>, R = H: 99%, 89% ee  
 Ar = *p*-BrC<sub>6</sub>H<sub>4</sub>, R = H: 97%, 92% ee  
 Ar = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, R = H: 96%, 87% ee  
 Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R = H: 87%, 91% ee  
 Ar = *p*-Tol, R = H: 94%, 90% ee  
 Ar = 2-Naph, R = H: 90%, 73% ee  
 Ar = 2-furyl, R = H: 93%, 89% ee  
 Ar = Ph, R = Me: 79%, 87% ee
- Ar = , R = H: 89%, 91% ee  
 Ar = , R = H: 89%, 85% ee



**Scheme 9** Michael addition of diethylmalonates to (hetero)aromatic nitroalkenes in the presence of a polysulfonate supported chiral diamine-nickel catalyst.

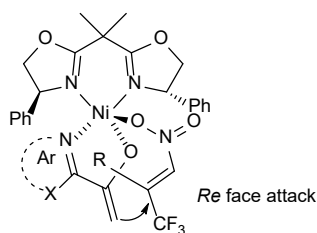
## 2.2. Other nucleophiles

In addition to 1,3-dicarbonyl compounds, a range of other nucleophiles have been enantioselectively added to nitroalkenes. For example, Fu et al. reported in 2016 the first example of enantioselective Michael addition of 2-acetyl azaarenes to  $\beta$ -trifluoromethyl- $\beta$ -disubstituted nitroalkenes which was achieved through catalysis with a chiral nickel complex.<sup>28</sup> The latter was in situ generated from 10 mol% of Ni(acac)<sub>2</sub> and 11 mol% of chiral bisoxazoline ligand **9** in isopropanol as solvent. Under these conditions, a wide range of 2-acetyl azaarenes reacted at 0 °C with  $\beta$ , $\beta$ -disubstituted nitroalkenes to afford the corresponding chiral functionalized products bearing a trifluoromethyl all-carbon quaternary chiral center with good to quantitative yields (62-99%) and uniformly high enantioselectivities (85->99% ee), as illustrated in Scheme 10. Various 2-acetyl azaarenes exhibiting a five-membered *N*-heterocycle were compatible, leading to the desired products with excellent enantioselectivities (96-99% ee), although the reactivity was dramatically dependent on the structure of the *N*-heterocycle. Among heterocycles, 2-acetyl thiazole was the most suitable substrate, affording the corresponding enantiopure product (99% ee) in quantitative yield (99%). Moreover, substrates bearing six-membered *N*-heterocycles, such as pyrazine, pyrimidine, quinoline and quinoxaline, were tolerated, leading to the desired products with high ee values (85-99% ee) albeit after longer reaction times. The formed densely functionalized products constituted potentially useful intermediates for the synthesis of important molecules in medicinal chemistry. The authors explained the stereoselectivity of the reaction by the transition state depicted in Scheme 10 arisen from the interaction of the in situ generated chiral Lewis acid catalyst with the 2-acetyl azaarene, resulting in a nickel enolate. Moreover, the nitroalkene was also activated through coordination of the nitro group to the chiral nickel complex. The activated enolate preferably approached the *E*-configured nitroalkene from the less sterically hindered *Re* face.



2-azaaryl = 2-oxazolyl, R = Ph: 59%, 97% ee  
 2-azaaryl = 2-thiazolyl, R = Ph: 99%, 99% ee  
 2-azaaryl = *N*-methyl-2-imidazolyl, R = Ph: 81%, 96% ee  
 2-azaaryl = 2-benzothiazolyl, R = Ph: 70%, 97% ee  
 2-azaaryl = 2-pyrazinyl, R = Ph: 92%, 99% ee  
 2-azaaryl = 2-pyridinyl, R = Ph: 67%, 85% ee  
 2-azaaryl = 2-quinolinyl, R = Ph: 71%, 97% ee  
 2-azaaryl = 2-quinoxaliny, R = Ph: 72%, 97% ee  
 2-azaaryl = 2-thiazolyl, R = *p*-Tol: 97%, 99% ee  
 2-azaaryl = 2-thiazolyl, R = *p*-MeOC<sub>6</sub>H<sub>4</sub>: 81%, 99% ee  
 2-azaaryl = 2-thiazolyl, R = *m*-Tol: 85%, 93% ee  
 2-azaaryl = 2-thiazolyl, R = *m*-MeOC<sub>6</sub>H<sub>4</sub>: 91%, 99% ee  
 2-azaaryl = 2-thiazolyl, R = *p*-FC<sub>6</sub>H<sub>4</sub>: 71%, 97% ee  
 2-azaaryl = 2-thiazolyl, R = *p*-ClC<sub>6</sub>H<sub>4</sub>: 86%, 94% ee  
 2-azaaryl = 2-thiazolyl, R = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>: 80%, 98% ee  
 2-azaaryl = 2-thiazolyl, R = *m*-FC<sub>6</sub>H<sub>4</sub>: 76%, 99% ee  
 2-azaaryl = 2-thiazolyl, R = *m*-ClC<sub>6</sub>H<sub>4</sub>: 65%, >99% ee  
 2-azaaryl = 2-thiazolyl, R = *m*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>: 79%, 98% ee  
 2-azaaryl = 2-thiazolyl, R = biphenyl: 62%, 99% ee  
 2-azaaryl = 2-thiazolyl, R = 3-thienyl: 73%, 93% ee  
 2-azaaryl = 2-thiazolyl, R = Cy: 72%, 99% ee  
 2-azaaryl = 2-thiazolyl, R = *n*-Oct: 79%, 96% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-Tol: 94%, 97% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-MeOC<sub>6</sub>H<sub>4</sub>: 95%, 96% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-ClC<sub>6</sub>H<sub>4</sub>: 93%, 91% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>: 86%, 94% ee  
 2-azaaryl = 2-pyrazinyl, R = *p*-MeOC<sub>6</sub>H<sub>4</sub>: 78%, 99% ee  
 2-azaaryl = 2-pyrazinyl, R = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>: 90%, 98% ee

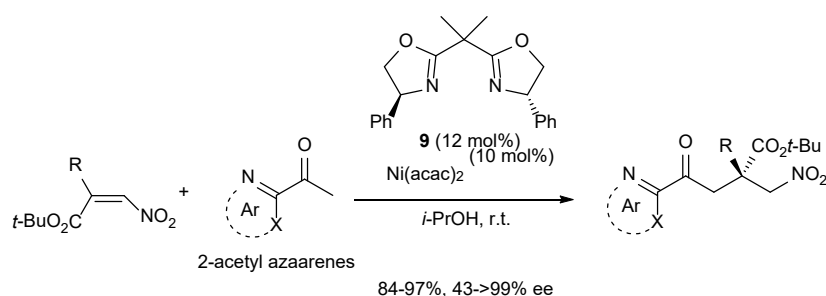
possible transition state:



**Scheme 10** Michael addition of 2-acetyl azaarenes to  $\beta$ -trifluoromethyl- $\beta$ -disubstituted nitroalkenes.

Later in 2017, this group applied the same catalyst system composed of 10 mol% of Ni(acac)<sub>2</sub> and 12 mol% of chiral bisoxazoline ligand **9** to promote related asymmetric Michael addition of 2-acetyl azaarenes to  $\alpha$ -substituted  $\beta$ -nitroacrylates.<sup>29</sup> As shown in Scheme 11, the reaction was also performed in isopropanol as solvent but in this case at room temperature, allowing the synthesis of a wide variety of chiral aromatic *N*-heterocycle-containing compounds bearing an all-carbon quaternary stereocenter in high yields (84-97%) with moderate to excellent enantioselectivities (43->99% ee). Actually, the enantioselectivities were found generally very high (93->99% ee) excepted in the reaction of methyl- and *n*-heptyl-substituted substrates (R = Me, *n*-Hept) which afforded the desired products with only moderate enantioselectivities (66% and 43% ee, respectively). However, the bulky cyclohexyl-substituted nitroacrylate (R = Cy) reacted with 94% ee, suggesting that a steric effect could be mainly responsible for the excellent enantioselectivity of the reaction. The products

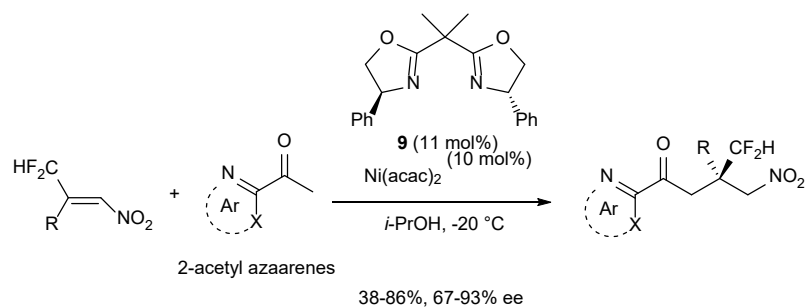
could be easily converted into diverse useful synthetic intermediates, such as chiral  $\beta^{2,2}$ -amino ester, pyrrolidine, succinate,  $\gamma$ -lactam, and  $\gamma$ -lactone derivatives bearing all-carbon quaternary stereocenters.



2-azaaryl = 2-pyridinyl, R = *p*-Tol: 93%, 97% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-MeOC<sub>6</sub>H<sub>4</sub>: 93%, 98% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-FC<sub>6</sub>H<sub>4</sub>: 95%, 98% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-BrC<sub>6</sub>H<sub>4</sub>: 93%, 99% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>: 94%, 97% ee  
 2-azaaryl = 2-pyridinyl, R = *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>: 97%, 97% ee  
 2-azaaryl = 2-pyridinyl, R = 2-furyl: 92%, 95% ee  
 2-azaaryl = 2-pyridinyl, R = 2-thienyl: 96%, 96% ee  
 2-azaaryl = 2-pyridinyl, R = styryl: 95%, 95% ee  
 2-azaaryl = 5-Me-2-pyridinyl, R = Ph: 90%, 93% ee  
 2-azaaryl = 5-Br-2-pyridinyl, R = Ph: 94%, 98% ee  
 2-azaaryl = 2-pyridinyl, R = Me: 95%, 66% ee  
 2-azaaryl = 2-pyridinyl, R = *n*-Hept: 93%, 43% ee  
 2-azaaryl = 2-pyridinyl, R = Cy: 84%, 94% ee  
 2-azaaryl = 2-pyrazinyl, R = Ph: 85%, 99% ee  
 2-azaaryl = 2-pyrimidinyl, R = Ph: 86%, 93% ee  
 2-azaaryl = 2-quinolinyl, R = Ph: 97%, 99% ee  
 2-azaaryl = 2-quinoxalyl, R = Ph: 90%, 98% ee  
 2-azaaryl = 2-oxazolyl, R = Ph: 86%, 98% ee  
 2-azaaryl = 2-thiazolyl, R = Ph: 92%, 99% ee  
 2-azaaryl = *N*-Me-2-imidazolyl, R = Ph: 92%, >99% ee  
 2-azaaryl = *N*-Bn-2-imidazolyl, R = Ph: 85%, 99% ee  
 2-azaaryl = *N*-Me-2-imidazolyl, R = 2-furyl: 85%, >99% ee  
 2-azaaryl = *N*-Me-2-imidazolyl, R = 2-thienyl: 88%, >99% ee

**Scheme 11** Michael addition of 2-acetyl azaarenes to  $\alpha$ -substituted  $\beta$ -nitroacrylates.

In 2018, these authors also investigated the asymmetric Michael addition of 2-acetyl azaarenes to  $\beta$ -difluoromethyl- $\beta$ -disubstituted nitroalkenes in the presence of the same catalyst system (Scheme 12).<sup>30</sup> The process was also performed in isopropanol as solvent albeit at a lower temperature (-20 °C), leading to chiral difluoromethylated products bearing an all-carbon quaternary stereocenter with both moderate to high yields (38-86%) and enantioselectivities (67-93% ee). A variety of azaarenes containing a five-membered *N*-heterocycle reacted with moderate to high enantioselectivities (67-93% ee) with 2-acetyl *N*-methyl 2-imidazole furnishing the best result (93% ee). In addition, substrates exhibiting six-membered *N*-heterocycles, such as pyrazine, quinoline, 2-benzopyrazine and quinoxaline, yielded the corresponding products with 71-80% ee. Concerning the nitroalkene partner, aromatic substituents bearing either electron-donating or electron-withdrawing groups at the *para*- or *meta*-position of the phenyl ring, reacted smoothly to afford the corresponding products with 71-83% ee. However, the presence of an *ortho*-substituent on the phenyl ring of the nitroalkene was not compatible since no reaction took place related to steric hindrance. The authors also showed that alkyl-substituted nitroalkenes reacted albeit with low ee values (20% ee). Once again, the formed chiral functionalized heterocycles exhibiting a quaternary stereocenter represent potential targets for medicinal chemistry. The remarkable efficiency of readily available and inexpensive catalyst **9** is demonstrated by the results illustrated in Schemes 10-12 achieved under mild reaction conditions and revealing an extremely broad scope.

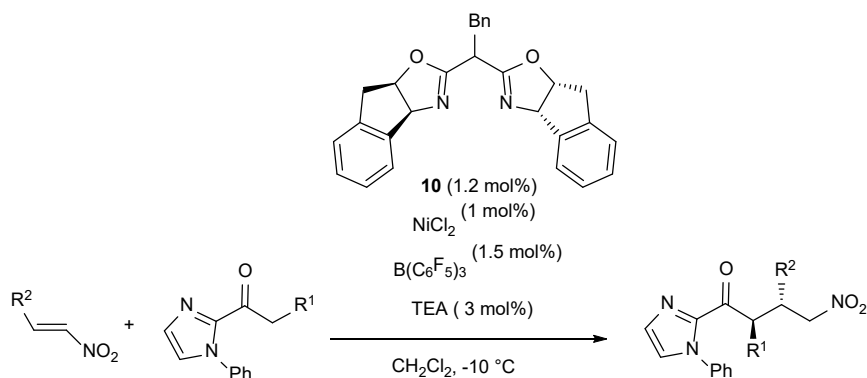


- 2-azaaryl = 2-oxazolyl, R = Ph: 58%, 71% ee
- 2-azaaryl = 2-thiazolyl, R = Ph: 48%, 81% ee
- 2-azaaryl = *N*-Me-2-imidazolyl, R = Ph: 68%, 93% ee
- 2-azaaryl = 2-benzoxazolyl, R = Ph: 40%, 67% ee
- 2-azaaryl = 2-benzothiazolyl, R = Ph: 48%, 75% ee
- 2-azaaryl = 2-pyrazinyl, R = Ph: 76%, 79% ee
- 2-azaaryl = 2-quinolinyl, R = Ph: 45%, 71% ee
- 2-azaaryl = 2-benzopyrazinyl, R = Ph: 38%, 80% ee
- 2-azaaryl = 2-pyridinyl, R = *p*-Tol: 84%, 76% ee
- 2-azaaryl = 2-pyridinyl, R = *p*-MeOC<sub>6</sub>H<sub>4</sub>: 81%, 83% ee
- 2-azaaryl = 2-pyridinyl, R = *p*-ClC<sub>6</sub>H<sub>4</sub>: 86%, 77% ee
- 2-azaaryl = 2-pyridinyl, R = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>: 74%, 81% ee
- 2-azaaryl = 2-pyridinyl, R = *m*-MeOC<sub>6</sub>H<sub>4</sub>: 76%, 71% ee
- 2-azaaryl = 2-pyridinyl, R = *m*-ClC<sub>6</sub>H<sub>4</sub>: 85%, 77% ee
- 2-azaaryl = 2-pyridinyl, R = *n*-Hept: 77%, 20% ee

**Scheme 12** Michael addition of 2-acetyl azaarenes to  $\beta$ -difluoromethyl- $\beta$ -disubstituted nitroalkenes.

In 2022, Wu et al. reported a rare example of enantioselective Michael addition of  $\alpha$ -substituted acyl imidazoles to nitroalkenes catalyzed by a nickel bisoxazoline complex.<sup>31</sup> The reaction employed only 1 mol% of NiCl<sub>2</sub> as precatalyst, 1.2 mol% of chiral bisoxazoline **10** as ligand and 1.5 mol% of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> as co-catalyst in dichloromethane as solvent. Performed at -10 °C in the presence of TEA as base, it afforded a wide diversity of functionalized chiral acyl imidazoles with both moderate to excellent yields (38-99%) and enantioselectivities (60-98% ee) combined with low to complete diastereoselectivities (13-98% de), as presented in Scheme 13. It was found that the use of strong Lewis acid B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> as co-catalyst proved to be vital to the success of this process. A wide range of nitroalkenes were compatible to the catalyst system but alkyl-substituted ones (R<sup>2</sup> = *n*-Bu, 2-styryl) reacted with lower yields (38-46%), diastereo- (60% de) and enantioselectivities (57-79% ee) than (hetero)aryl-substituted nitroalkenes. Various substituted acyl imidazoles were also tolerated but an alkyl-substituted substrate (R<sup>1</sup> = Bn) reacted with a lower yield (74%) than aryl-substituted compounds. An heteroaryl-substituted acyl imidazole (R<sup>1</sup> = 2-thienyl) led to the corresponding product with a lower ee value (72% ee) than aryl-substituted substrates. It was also found that acetyl-imidazole (R<sup>1</sup> = H) also provided the product albeit in very low enantioselectivity (13% ee).



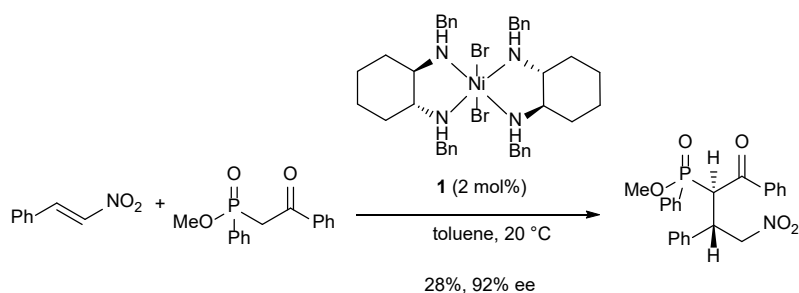


38-99%, 60-98% de, 13-98% ee

$R^1 = R^2 = \text{Ph}$ : 98%, 98% de, 95% ee  
 $R^1 = \text{Ph}, R^2 = p\text{-FC}_6\text{H}_4$ : 90%, 96% de, 92% ee  
 $R^1 = \text{Ph}, R^2 = p\text{-ClC}_6\text{H}_4$ : 98%, 96% de, 92% ee  
 $R^1 = \text{Ph}, R^2 = p\text{-BrC}_6\text{H}_4$ : 98%, 94% de, 93% ee  
 $R^1 = \text{Ph}, R^2 = p\text{-O}_2\text{NC}_6\text{H}_4$ : 98%, 91% de, 91% ee  
 $R^1 = \text{Ph}, R^2 = o\text{-ClC}_6\text{H}_4$ : 82%, 88% de, 92% ee  
 $R^1 = \text{Ph}, R^2 = 3,4\text{-Cl}_2\text{C}_6\text{H}_3$ : 90%, 92% de, 85% ee  
 $R^1 = \text{Ph}, R^2 = p\text{-Tol}$ : 92%, 98% de, 93% ee  
 $R^1 = \text{Ph}, R^2 = p\text{-MeOC}_6\text{H}_4$ : 96%, 98% de, 98% ee  
 $R^1 = \text{Ph}, R^2 = o\text{-Tol}$ : 95%, 98% de, 93% ee  
 $R^1 = \text{Ph}, R^2 = m\text{-Tol}$ : 98%, 98% de, 94% ee  
 $R^1 = \text{Ph}, R^2 = 1\text{-Naph}$ : 98%, 98% de, 92% ee  
 $R^1 = \text{Ph}, R^2 = 2\text{-furyl}$ : 94%, 98% de, 91% ee  
 $R^1 = \text{Ph}, R^2 = 2\text{-thienyl}$ : 99%, 96% de, 94% ee  
 $R^1 = \text{Ph}, R^2 = n\text{-Bu}$ : 38%, 60% de, 60/79% ee  
 $R^1 = \text{Ph}, R^2 = 2\text{-styryl}$ : 46%, 60% de, 72/57% ee  
 $R^1 = p\text{-FC}_6\text{H}_4, R^2 = \text{Ph}$ : 94%, 98% de, 93% ee  
 $R^1 = p\text{-ClC}_6\text{H}_4, R^2 = \text{Ph}$ : 94%, 96% de, 92% ee  
 $R^1 = p\text{-BrC}_6\text{H}_4, R^2 = \text{Ph}$ : 82%, 98% de, 95% ee  
 $R^1 = o\text{-ClC}_6\text{H}_4, R^2 = \text{Ph}$ : 91%, 98% de, 92% ee  
 $R^1 = o\text{-BrC}_6\text{H}_4, R^2 = \text{Ph}$ : 96%, 98% de, 91% ee  
 $R^1 = m\text{-BrC}_6\text{H}_4, R^2 = \text{Ph}$ : 96%, 98% de, 86% ee  
 $R^1 = p\text{-Tol}, R^2 = \text{Ph}$ : 94%, 98% de, 91% ee  
 $R^1 = p\text{-MeOC}_6\text{H}_4, R^2 = \text{Ph}$ : 98%, 98% de, 94% ee  
 $R^1 = o\text{-Tol}, R^2 = \text{Ph}$ : 99%, 98% de, 94% ee  
 $R^1 = m\text{-Tol}, R^2 = \text{Ph}$ : 95%, 98% de, 92% ee  
 $R^1 = 1\text{-Naph}, R^2 = \text{Ph}$ : 99%, 98% de, 80% ee  
 $R^1 = 2\text{-Naph}, R^2 = \text{Ph}$ : 92%, 96% de, 96% ee  
 $R^1 = \text{Bn}, R^2 = \text{Ph}$ : 74%, 92% de, 90% ee  
 $R^1 = 2\text{-thienyl}, R^2 = \text{Ph}$ : 84%, 98% de, 72% ee  
 $R^1 = \text{H}, R^2 = \text{Ph}$ : 69%, 13% ee

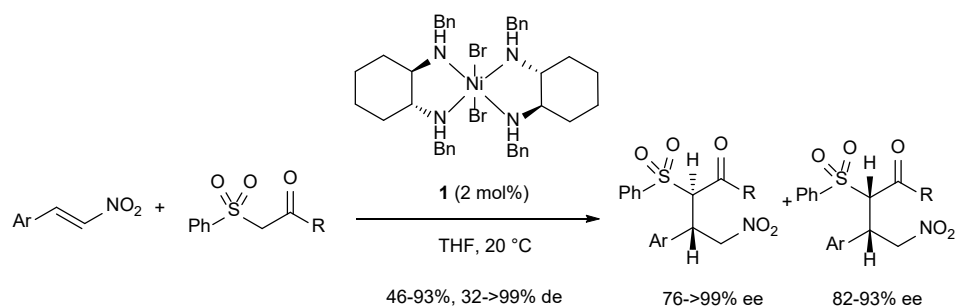
**Scheme 13** Michael addition of  $\alpha$ -substituted acyl imidazoles to nitroalkenes.

Earlier in 2017, Sibiryakova et al. investigated the asymmetric Michael addition of a racemic  $\beta$ -ketophosphinate to  $\beta$ -phenyl nitroalkene<sup>32</sup> in the presence of 2 mol% of preformed chiral nickel complex **1** which was introduced in 2005 by Evans and Seidel.<sup>18</sup> The reaction was performed at 20 °C in toluene as solvent, allowing the synthesis of the corresponding chiral keto nitrophosphinate as a mixture of three diastereomers (3:2:1). Among them, the major diastereomer was obtained with 92% ee and 28% yield (Scheme 14).



**Scheme 14** Michael addition of a  $\beta$ -ketophosphinate to  $\beta$ -phenyl nitroalkene.

Chiral functionalized sulfones constitute key intermediates in organic synthesis and especially in medicinal chemistry.<sup>33</sup> In 2019, Reznikov et al. described a simple access to chiral 4-nitro-2-sulfonylbutan-1-ones bearing two stereocenters through asymmetric Michael addition of the corresponding  $\beta$ -ketosulfones to nitrostyrenes catalyzed at 20 °C in THF as solvent by 2 mol% of nickel complex **1** (Scheme 15).<sup>34</sup> Several functionalized chiral sulfones were synthesized as mixtures of two diastereomers with variable yields (46-93%), moderate to excellent diastereoselectivities (32->99% de) and good to high enantioselectivities (76->99% ee) for both diastereomers. In some cases, a complete diastereoselectivity was observed while it was found that the presence of substituents in the 2- or 3-position of the aryl ring of sulfones or nitroalkenes decreased the diastereoselectivity of the reaction. Actually, it was established that the Michael reaction itself was performed with high diastereoselectivity, but the Michael adducts could epimerize at the C-2 position at a significant rate.

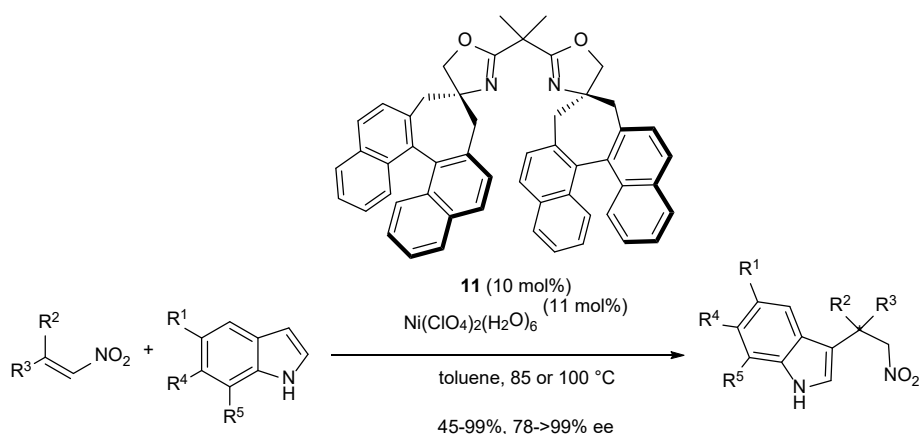


Ar = R = Ph: 77%, >99% de, 94% ee  
 Ar = Ph, R = *p*-ClC<sub>6</sub>H<sub>4</sub>: 72%, >99% de, 92% ee  
 Ar = Ph, R = *m*-MeOC<sub>6</sub>H<sub>4</sub>: 46%, 32% de, 88% ee (major), 82% ee (minor)  
 Ar = Ph, R = 1-Ad: 67%, >99% de, 93% ee  
 Ar = *p*-FC<sub>6</sub>H<sub>4</sub>, R = Ph: 74%, >99% de, 96% ee  
 Ar = *p*-ClC<sub>6</sub>H<sub>4</sub>, R = Ph: 71%, >99% de, >99% ee  
 Ar = *o*-ClC<sub>6</sub>H<sub>4</sub>, R = Ph: 93%, 48% de, 92% ee (major), 93% ee (minor)  
 Ar = *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, R = Ph: 65%, >99% de, 76% ee  
 Ar = *m*-MeOC<sub>6</sub>H<sub>4</sub>, R = Ph: 52%, 84% de, 78% ee (major), 89% ee (minor)

**Scheme 15** Michael addition of  $\beta$ -ketosulfones to nitrostyrenes.

In 2022, Shi et al. disclosed the synthesis of a novel type of chiral spiro-fused bisoxazoline ligands possessing a deep chiral pocket.<sup>35</sup> Among them, chiral ligand **11** employed at 10 mol% of catalyst loading was found to be highly efficient when combined with 11 mol% of Ni(ClO<sub>4</sub>)<sub>2</sub>·(H<sub>2</sub>O)<sub>6</sub> as precatalyst to promote enantioselective Michael-type Friedel–Crafts reaction between indoles and  $\beta$ -trifluoromethyl- $\beta$ -disubstituted nitroalkenes (R<sup>2</sup> = CF<sub>3</sub>). As presented in Scheme 16, the reaction carried out at 85 or 100 °C in toluene as solvent resulted in the formation of the corresponding chiral indole derivatives bearing a trifluoromethylated all-carbon quaternary stereocenter with moderate to quantitative yields (45-99%) and generally high enantioselectivities (78->99% ee). The catalyst system tolerated the presence of different substituents at the C5 and C6 positions of the indole ring, delivering the desired products with remarkable enantioselectivities. In addition, a

methyl and a methoxy group were compatible at the C7 position, delivering the products with excellent ee values (96->99% ee) albeit combined with decreased yields (45-76%) related to steric hindrance. Concerning the  $\beta$ -trifluoromethyl- $\beta$ -disubstituted nitroalkene partner, a *para*-substituted (*E*)-1-phenyl-1-trifluoromethyl-2-nitroethene bearing an electron-donating group on the phenyl ring ( $R^3 = p\text{-Tol}$ ) reacted with 96% ee while nitroalkenes bearing an electron-withdrawing group delivered the corresponding products ( $R^3 = p\text{-BrC}_6\text{H}_4$ ,  $p\text{-ClC}_6\text{H}_4$ ,  $p\text{-FC}_6\text{H}_4$ ) with generally lower ee values (78-96% ee). Moreover, *meta*-substituted (*E*)-1-phenyl-1-trifluoromethyl-2-nitroethenes with either electron-donating or electron-withdrawing groups on the phenyl ring provided excellent results (98->99% ee). Interestingly, alkyl-substituted nitroalkenes ( $R^3 = \text{BnCH}_2$ , *n*-Dec) also reacted smoothly to give the desired products with high enantioselectivities (90-96% ee). The scope of the methodology could also be extended to a  $\beta$ -difluoromethyl- $\beta$ -disubstituted nitroalkene ( $R^2 = \text{CF}_2\text{H}$ ) which delivered the corresponding indole with 98% ee.



$R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}: 99\%, >99\% \text{ ee}$   
 $R^1 = \text{OMe}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = R_5 = \text{H}: 99\%, 97\% \text{ ee}$   
 $R^1 = \text{F}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = R_5 = \text{H}: 69\%, 98\% \text{ ee}$   
 $R^1 = \text{Br}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = R_5 = \text{H}: 54\%, 87\% \text{ ee}$   
 $R^1 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = \text{OMe}: 99\%, >99\% \text{ ee}$   
 $R^1 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = \text{OBn}: 98\%, >99\% \text{ ee}$   
 $R^1 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = \text{Me}: 96\%, >99\% \text{ ee}$   
 $R^1 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = \text{Br}: 93\%, >99\% \text{ ee}$   
 $R^1 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = \text{Cl}: 99\%, >99\% \text{ ee}$   
 $R^1 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = \text{F}: 89\%, >99\% \text{ ee}$   
 $R^1 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_4 = \text{CO}_2\text{Me}: 87\%, >99\% \text{ ee}$   
 $R^1 = R_4 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_5 = \text{OMe}: 45\%, >99\% \text{ ee}$   
 $R^1 = R_4 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}, R_5 = \text{Me}: 76\%, 96\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}: 99\%, 96\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = p\text{-Tol}: 99\%, 96\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = p\text{-BrC}_6\text{H}_4: 99\%, 96\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = p\text{-ClC}_6\text{H}_4: 99\%, 89\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = p\text{-FC}_6\text{H}_4: 99\%, 78\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = m\text{-MeOC}_6\text{H}_4: 93\%, >99\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = m\text{-ClC}_6\text{H}_4: 69\%, 98\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = 2\text{-Napht}: 93\%, >99\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{BnCH}_2: 64\%, 90\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = n\text{-C}_{10}\text{H}_{21}: 94\%, 96\% \text{ ee}$   
 $R^1 = R_4 = R_5 = \text{H}, R_2 = \text{CF}_3, R^3 = \text{Ph}: 96\%, 98\% \text{ ee}$

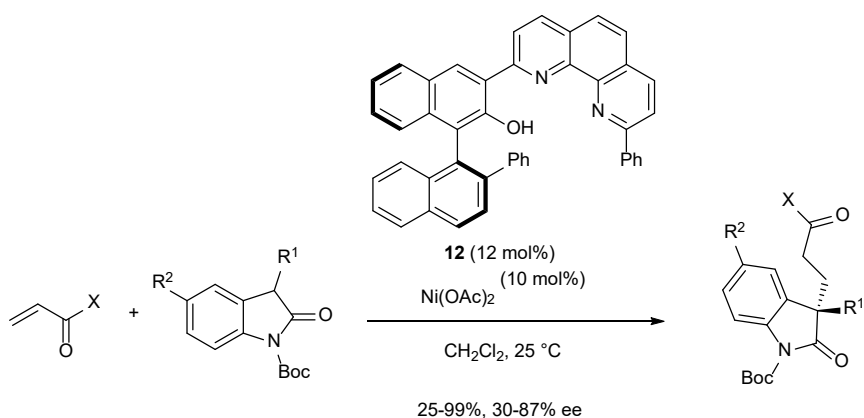
**Scheme 16** Michael-type Friedel–Crafts reaction of indoles with  $\beta\text{-CF}_3/\text{CF}_2\text{H}$ - $\beta$ -disubstituted nitroalkenes.

### 3. Conjugate additions to $\alpha,\beta$ -unsaturated carbonyl compounds and derivatives

#### 3.1. Carbon nucleophiles

Chiral oxindoles represent an important class of products, which are widely present in nature and exhibit many biological activities.<sup>36</sup> Among these compounds, oxindoles exhibiting an all-carbon quaternary center at the 3-position constitute ubiquitous structures present in a broad range of natural alkaloids. One of the most useful route to these molecules is

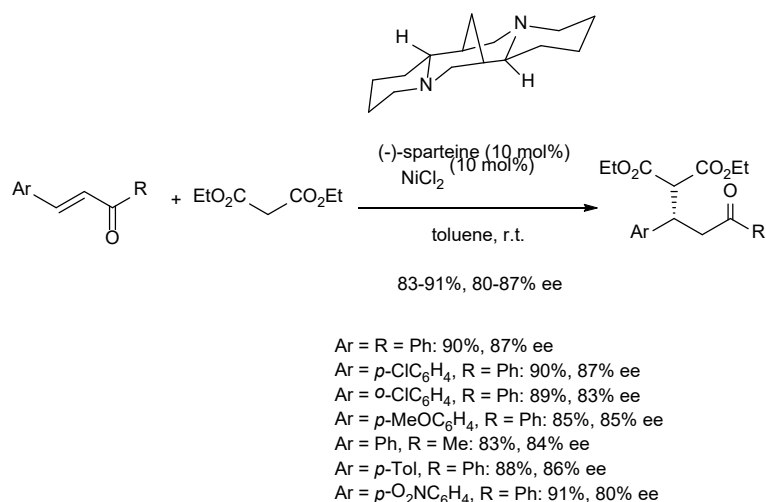
based on enantioselective Michael addition of 3-substituted oxindole derivatives to  $\alpha,\beta$ -unsaturated carbonyl compounds. In 1988, Soai et al. reported the first enantioselective nickel-catalyzed conjugate addition involving  $\alpha,\beta$ -unsaturated carbonyl compounds as electrophiles which was performed in the presence of a chiral ephedrine-derived ligand.<sup>10</sup> Ever since, many types of other chiral ligands have been successfully applied to promote asymmetric nickel-catalyzed Michael additions including those allowing the synthesis of chiral oxindoles. In an example reported in 2016, novel chiral N,N,O-tridentate phenanthroline ligand **12** was combined for the first time by Naganawa and Nishiyama with nickel to promote enantioselective Michael additions of *N*-Boc-oxindoles to methyl vinyl ketone (X = Me), as shown in Scheme 17.<sup>37</sup> Indeed, in the presence of a combination of 12 mol% of this ligand with 10 mol% of Ni(OAc)<sub>2</sub>, the reaction occurred at 25 °C in dichloromethane as solvent to provide the corresponding chiral indole derivatives bearing an all-carbon quaternary center in good to quantitative yields (77-99%) and moderate to high ee values (65-87% ee). In addition, the scope of the reaction could be extended to other Michael acceptors, such as acrolein (X = H) and phenyl vinyl ketone (X = Ph), albeit the corresponding products were produced with lower ee values (30-43% ee). It is interesting to note that when the aryl substituent (R<sup>1</sup>) of *N*-Boc-oxindole was replaced by a methyl group, the reaction of *N*-Boc-3-methyloxindole (R<sup>1</sup> = Me, R<sup>2</sup> = H) occurred to give the corresponding product with 70% ee albeit with a low yield (25%) probably due to the weaker acidity of the  $\alpha$ -carbon of the carbonyl moiety than that of *N*-Boc-3-phenyloxindole (R<sup>1</sup> = Ph, R<sup>2</sup> = H). It is also important to mention that this work represented the first application of chiral ligand **12** in nickel asymmetric catalysis.



- R<sup>1</sup> = Ph, R<sub>2</sub> = H, X = OMe: 92%, 87% ee
- R<sup>1</sup> = *p*-Tol, R<sub>2</sub> = H, X = OMe: 97%, 87% ee
- R<sup>1</sup> = *p*-PhC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = H, X = OMe: 85%, 70% ee
- R<sup>1</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = H, X = OMe: 77%, 71% ee
- R<sup>1</sup> = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = H, X = OMe: 99%, 65% ee
- R<sup>1</sup> = Me, R<sub>2</sub> = H, X = OMe: 25%, 70% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = Me, X = OMe: 89%, 70% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = X = OMe: 85%, 78% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = F, X = OMe: 95%, 77% ee
- R<sup>1</sup> = *p*-Tol, R<sub>2</sub> = Me, X = OMe: 80%, 80% ee
- R<sup>1</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = F, X = OMe: 91%, 81% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = H, X = Me: 92%, 87% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = X = H: 35%, 30% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = H, X = Ph: 94%, 43% ee

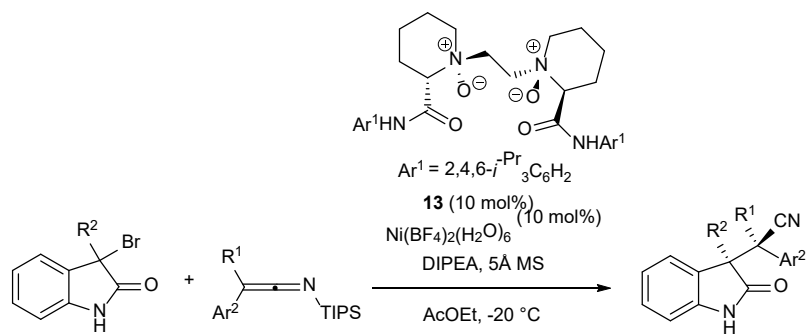
**Scheme 17** Michael addition of *N*-Boc-oxindoles to methyl vinyl ketone.

In 2017, Chopade demonstrated that (-)-sparteine could be an efficient and inexpensive chiral bidentate ligand of nickel to promote asymmetric Michael additions of diethylmalonate to  $\alpha,\beta$ -unsaturated ketones.<sup>38</sup> As presented in Scheme 18, using 10 mol% of this ligand combined with the same quantity of NiCl<sub>2</sub> as precatalyst in toluene as solvent allowed the reaction to occur at room temperature, leading to the corresponding chiral products with both good to high yields (83-91%) and enantioselectivities (80-87% ee). Advantages of this novel methodology were related to its mild reaction conditions, simple and cheap catalyst, and easy work-up procedure.



**Scheme 18** Michael addition of diethylmalonate to  $\alpha,\beta$ -unsaturated ketones.

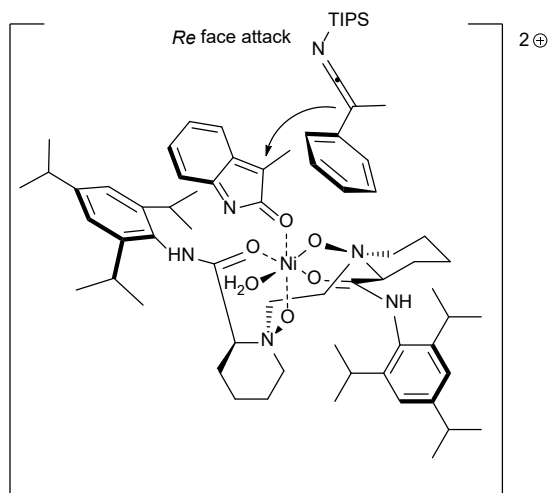
Silyl ketene imines are  $\alpha$ -cyano carbanion equivalents which allow the synthesis of alkyl nitriles through condensation onto electrophiles. Among potential electrophiles are indol-2-ones which can be in situ generated from 3-bromooxindoles. In 2017, Feng and Liu described the first enantioselective conjugate addition of silyl ketene imines to indol-2-ones in situ generated from the corresponding 3-bromooxindoles.<sup>39</sup> The process was performed at -20 °C in the presence of a chiral nickel catalyst in situ generated from 10 mol% of Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and the same quantity of chiral *N,N'*-dioxide ligand **13** in acetonitrile as solvent. This methodology required the presence of DIPEA as base to provide the corresponding chiral functionalized  $\beta$ -alkyl nitriles bearing two congested vicinal all-carbon quaternary stereocenters with moderate to high yields (44-90%), uniformly excellent enantioselectivities (90-98% ee) and moderate to high diastereoselectivities (66-92% de), as shown in Scheme 19. A range of functional groups were tolerated, such as allyl, alkynyl, alkyl halide, silyl ether, sulfonamide and alkyl azide groups, allowing an easy transformation of the products into chiral pyrroloindoline and oxindole scaffolds often found in bioactive molecules. The authors proposed the transition state depicted in Scheme 19 in order to explain the stereochemical outcome of the reaction. An in situ generated indol-2-one could be activated after coordinating to the chiral nickel complex with its *Si* face shielded by the neighboring 2,4,6-triisopropylphenyl groups of the ligand. Consequently, the silyl ketene imine preferentially attacked from the *Re* face to afford the final product.



44-90%, 66-92% de, 90-98% ee

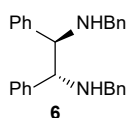
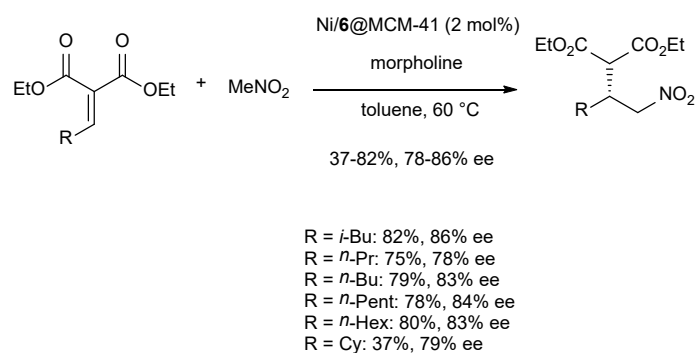
$\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 89%, 86% de, 95% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{Et}$ : 89%, 82% de, 92% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{Bn}$ : 90%, 84% de, 92% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{allyl}$ : 74%, 80% de, 90% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{MeC}(\text{CCH})_2$ : 77%, 80% de, 92% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{Cl}(\text{CF}_3)_2$ : 83%, 72% de, 92% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{Br}(\text{CH}_2)_2$ : 85%, 72% de, 93% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{I}(\text{CH}_2)_2$ : 77%, 72% de, 94% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{TBSO}(\text{CH}_2)_2$ : 77%, 72% de, 94% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{TsNH}(\text{CH}_2)_2$ : 68%, 84% de, 96% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{N}(\text{CH}_2)_2$ : 87%, 66% de, 92% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{N}(\text{CH}_2)_3$ : 81%, 72% de, 93% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = i\text{-Pr}$ : 64%, 82% de, 96% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = c\text{-Pent}$ : 81%, 84% de, 96% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{Cy}$ : 83%, 82% de, 97% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = c\text{-Hent}$ : 83%, 84% de, 98% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 89%, 86% de, 95% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Et}, \text{R}_2 = \text{Me}$ : 89%, 80% de, 92% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{allyl}, \text{R}_2 = \text{Me}$ : 85%, 80% de, 93% ee  
 $\text{Ar}^2 = m\text{-MeOC}_6\text{H}_4, \text{R}_1 = \text{R}_2 = \text{Me}$ : 72%, 88% de, 94% ee  
 $\text{Ar}^2 = o\text{-Tol}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 76%, 80% de, 96% ee  
 $\text{Ar}^2 = m\text{-Tol}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 88%, 80% de, 96% ee  
 $\text{Ar}^2 = p\text{-Tol}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 89%, 80% de, 94% ee  
 $\text{Ar}^2 = p\text{-FC}_6\text{H}_4, \text{R}_1 = \text{R}_2 = \text{Me}$ : 79%, 88% de, 94% ee  
 $\text{Ar}^2 = o\text{-BrC}_6\text{H}_4, \text{R}_1 = \text{R}_2 = \text{Me}$ : 73%, 90% de, 95% ee  
 $\text{Ar}^2 = m\text{-BrC}_6\text{H}_4, \text{R}_1 = \text{R}_2 = \text{Me}$ : 80%, 92% de, 96% ee  
 $\text{Ar}^2 = p\text{-BrC}_6\text{H}_4, \text{R}_1 = \text{R}_2 = \text{Me}$ : 81%, 88% de, 96% ee  
 $\text{Ar}^2 = 2\text{-Naph}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 89%, 88% de, 94% ee  
 $\text{Ar}^2 = 3\text{-thienyl}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 44%, 75% de, 92% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{R}_2 = \text{Me}$ : 82%, 86% de, 94% ee  
 $\text{Ar}^2 = \text{Ph}, \text{R}_1 = \text{Me}, \text{R}_2 = \text{C}_6\text{H}_4\text{O}$ : 61%, 82% de, 96% ee

proposed transition state (with Ar = Ph,  $\text{R}_1 = \text{R}_2 = \text{Me}$ ):



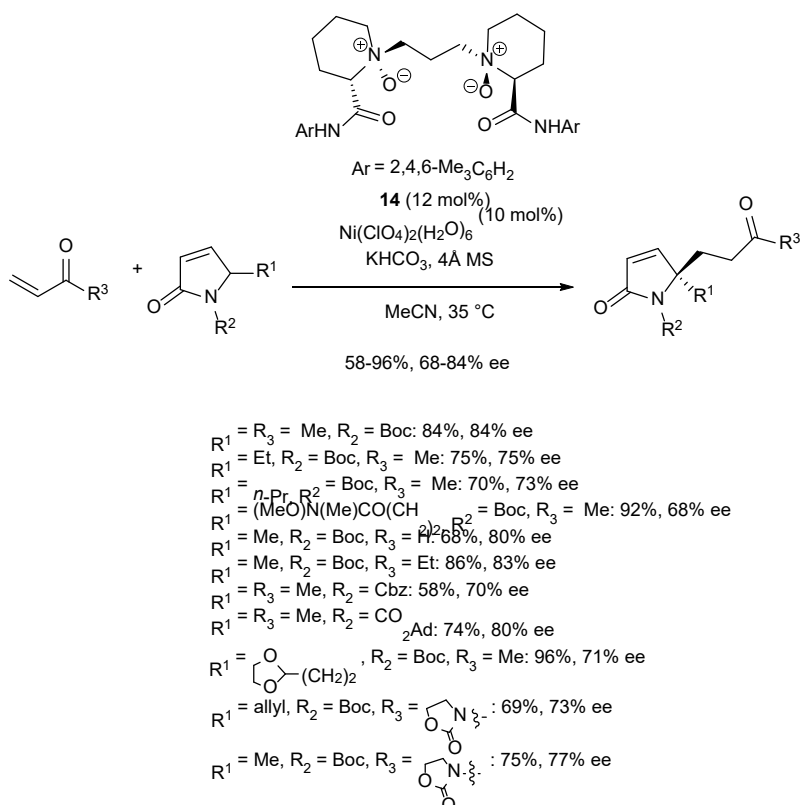
**Scheme 19** Conjugate addition of silyl ketene imines to indol-2-ones.

A chiral heterogeneous nickel catalyst consisting in a chiral nickel/1,2-diamine complex supported on MCM-41 was demonstrated by Ishitani and Kobayashi to be efficient in promoting enantioselective Michael addition of nitromethane to alkylidene malonates bearing aliphatic substituents (Scheme 20).<sup>25</sup> The reaction performed in toluene at 60 °C led to the corresponding chiral products with moderate to high yields (37-82%) and high enantioselectivities (78-86% ee). An advantage of this methodology was its compatibility with challenging alkylidene malonates bearing aliphatic substituents which often reacted in Michael additions with nitroalkanes with low enantioselectivities.



**Scheme 20** Michael addition of nitromethane to alkylidene malonates.

The  $\gamma,\gamma$ -disubstituted butyrolactam unit bearing a quaternary stereocenter constitutes the skeleton of many bioactive molecules. Consequently, the synthesis of this type of products is challenging. In this context, Wei and Xie developed in 2022 an enantioselective vinylogous Michael addition of  $\gamma$ -alkyl  $\alpha,\beta$ -unsaturated butyrolactams to  $\alpha,\beta$ -unsaturated carbonyl compounds, affording the desired chiral  $\gamma,\gamma$ -disubstituted butyrolactams in both moderate to high yields (58-96%) and enantioselectivities (68-84% ee), as illustrated in Scheme 21.<sup>40</sup> The process occurred at 35 °C in acetonitrile as solvent in the presence of  $\text{KHCO}_3$  as base under catalysis with 10 mol% of  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  and 12 mol% of chiral  $N,N'$ -dioxide ligand **14**. Butyrolactams exhibiting different  $\gamma$ -alkyl-substituents, such as methyl, ethyl, and *n*-propyl groups, reacted smoothly, but it was found that enantioselectivities decreased with more bulky substituents. Moreover, functionalities, such as amide, acetal and alkene, were tolerated, resulting in the formation of the corresponding products with moderate enantioselectivities (68-73% ee). On the other hand, different types of  $\alpha,\beta$ -unsaturated carbonyl compounds, including 3-acryloyl-2-oxazolidinone, acrolein and ethyl vinyl ketone, were compatible.

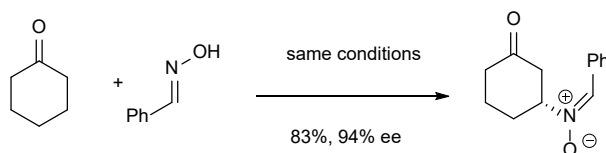
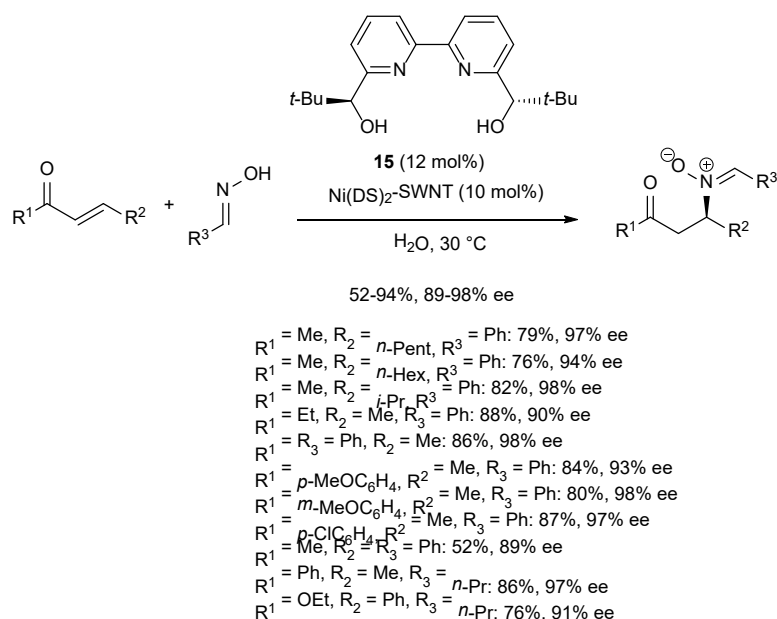


**Scheme 21** Vinylogous Michael addition of  $\gamma$ -alkyl  $\alpha,\beta$ -unsaturated butyrolactams to  $\alpha,\beta$ -unsaturated carbonyl compounds.

### 3.2. Other nucleophiles

In order to carry out asymmetric Michael reactions in water, Kobayashi et al. reported in 2018 the synthesis of nickel complexes derived from chiral 2,2'-bipyridine ligand **15** integrated with single-walled carbon nanotubes (SWNTs) to be applied in asymmetric catalysis in water.<sup>41</sup> Indeed, an homogenized combination of a nickel-based Lewis acid/surfactant-combined catalyst with single-walled carbon nanotubes was demonstrated to be an efficient promotor in asymmetric conjugate addition of aldoximes to  $\alpha,\beta$ -unsaturated carbonyl compounds performed in water at 30 °C. As shown in Scheme 22, the combination of 12 mol% of chiral ligand **15** with 10 mol% of homogeneous dispersion of Ni(DS)<sub>2</sub>-SWNT nanocomposite (DS = OSO<sub>3</sub>C<sub>12</sub>H<sub>25</sub>) allowed the Michael reaction to afford chiral nitrones with moderate to high yields (52-94%) and uniformly high ee values (89-98% ee).  $\alpha,\beta$ -Unsaturated ketones substituted by either aromatic or aliphatic groups reacted smoothly with excellent enantioselectivities. In all cases of substrates, the yields were  $\geq 76\%$  excepted for chalcone ( $\text{R}^1 = \text{R}^2 = \text{Ph}$ ) which led to the corresponding product with a lower yield (52%) albeit combined with a high ee value (89% ee). Moreover, the catalyst system tolerated aliphatic as well as aromatic aldoximes. A cyclic  $\alpha,\beta$ -unsaturated ketone such as cyclohexanone was also compatible, leading to the corresponding product in 83% yield and 94% ee. This catalyst system took advantage of the strong van der Waals force between SWNTs and carbon chains of dodecylsulfate to anchor Lewis acid cationic centers onto the surfaces of SWNTs without any perturbation of the cylindrical structure, unlike covalent SWNT modification.

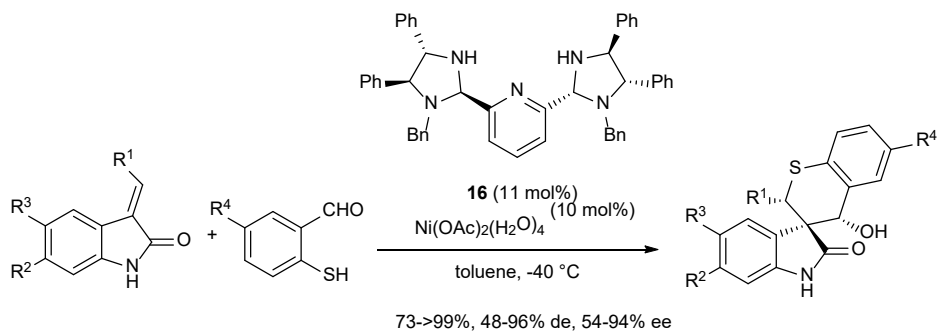




**Scheme 22** Conjugate addition of aldoximes to  $\alpha,\beta$ -unsaturated carbonyl compounds in water.

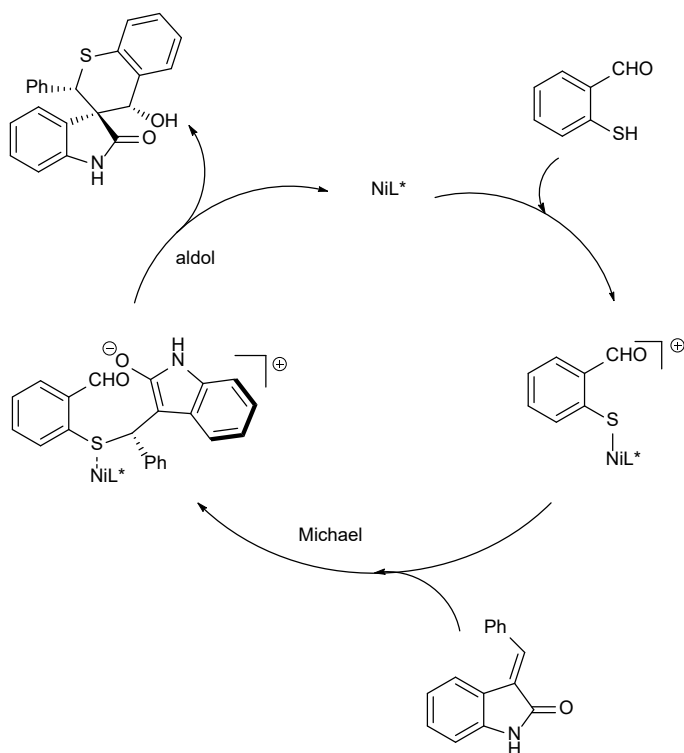
#### 4. Domino and tandem reactions based on a Michael addition

Domino and tandem processes allow very complex molecules to be synthesized through single-step procedures which do not require costly isolation and purification of intermediates.<sup>42</sup> Combining asymmetric nickel catalysis with these one-pot reactions suits perfectly the growing demand for more economic synthesis.<sup>43</sup> Since the first metal-catalyzed domino Michael/aldol reaction reported by Noyori et al. in 1996,<sup>44</sup> there have been numerous examples of domino reactions based on Michael additions.<sup>45</sup> Among recent examples involving nickel catalysts, the first example of enantioselective domino sulfa-Michael/aldol reaction between methyleneindolinones and thiosalicylaldehydes was described by Arai et al., in 2016 (Scheme 23).<sup>46</sup> The reaction was catalyzed at  $-40\text{ }^\circ\text{C}$  in toluene as solvent by a combination of 10 mol% of  $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  and 11 mol% of chiral bis-(imidazolidine)pyridine ligand **16** to produce the corresponding chiral thiochromanylspirooxindoles bearing three contiguous stereocenters with good to high yields (73-99%) and both moderate to high diastereo- (48-96% de) and enantioselectivities (54-94% ee). Along with aryl-substituted methyleneindolinones exhibiting either electron-withdrawing or electron-donating groups on the phenyl ring, an alkyl-substituted methyleneindolinone ( $R^1 = n\text{-Pr}$ ) was also compatible to give the desired product with 89% ee. Moreover, the presence of substituents, such as chloro and methyl groups, on the indolinone ring was well tolerated since the corresponding products were formed with 87-94% ee. On the other hand, the lowest ee value (54% ee) was obtained in the reaction of an ester-substituted methyleneindolinone ( $R^1 = \text{CO}_2\text{Et}$ ). These products constituted promising candidates for medicinal chemistry. The authors proposed the catalytic cycle depicted in Scheme 23, beginning with the formation of a nickel thiolate of the thiosalicylaldehyde. Then, the latter attacked the methyleneindolinone through a Michael addition to provide the corresponding enolate of indolinone. A subsequent intramolecular aldol reaction of this nickel enolate delivered the final thiochromanylspirooxindole along with regenerated catalyst.



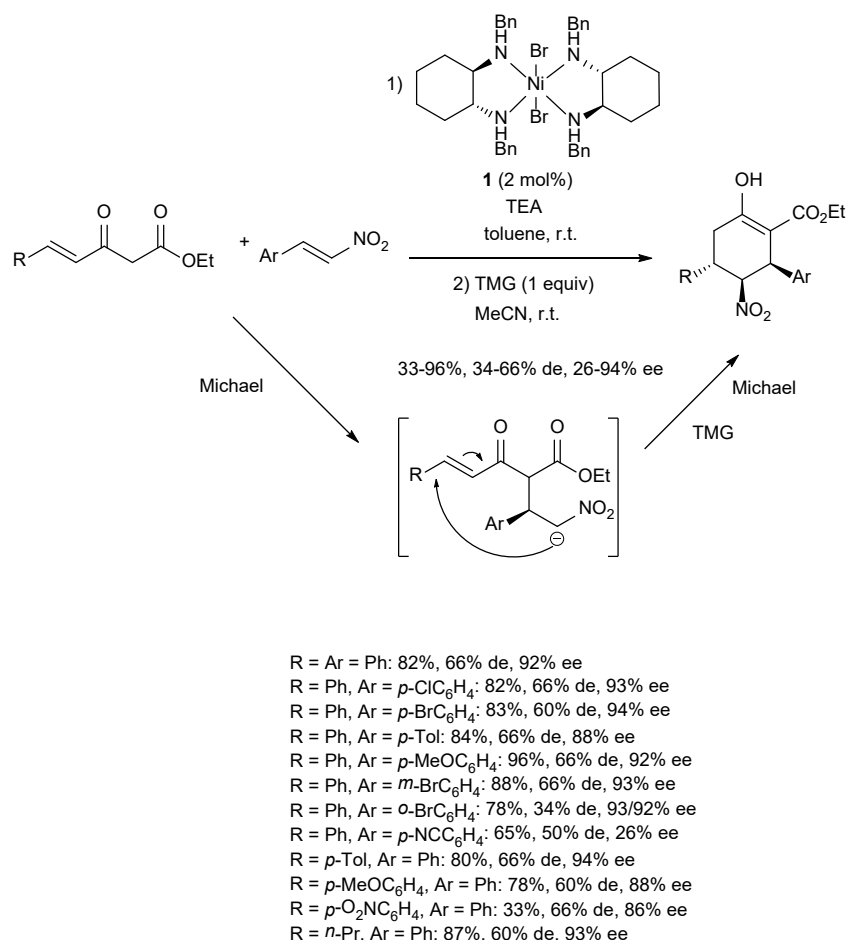
- R<sup>1</sup> = Ph, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: 99%, 86% de, 88% ee
- R<sup>1</sup> = *p*-BrC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: 94%, 86% de, 69% ee
- R<sup>1</sup> = *p*-ClC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: >99%, 86% de, 82% ee
- R<sup>1</sup> = *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: >99%, 72% de, 69% ee
- R<sup>1</sup> = *p*-Tol, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: 89%, 60% de, 81% ee
- R<sup>1</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: 85%, 96% de, 84% ee
- R<sup>1</sup> = *m*-ClC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: 98%, 48% de, 84% ee
- R<sup>1</sup> = *o*-BrC<sub>6</sub>H<sub>4</sub>, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: >99%, 96% de, 93% ee
- R<sup>1</sup> = *n*-Pr, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: >99%, 84% de, 89% ee
- R<sup>1</sup> = CO<sub>2</sub>Et, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H: >99%, 86% de, 54% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = Cl, R<sub>3</sub> = R<sub>4</sub> = H: >99%, 94% de, 94% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = H, R<sub>3</sub> = Cl: >99%, 86% de, 81% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = H, R<sub>3</sub> = Me: >99%, 74% de, 87% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = Cl: >99%, 90% de, 82% ee
- R<sup>1</sup> = Ph, R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = *t*-Bu: 73%, 96% de, 90% ee

proposed catalytic cycle (with R<sup>1</sup> = Ph, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H):



**Scheme 23** Domino sulfa-Michael/aldol reaction of methyleneindolinones with thioaldehydes.

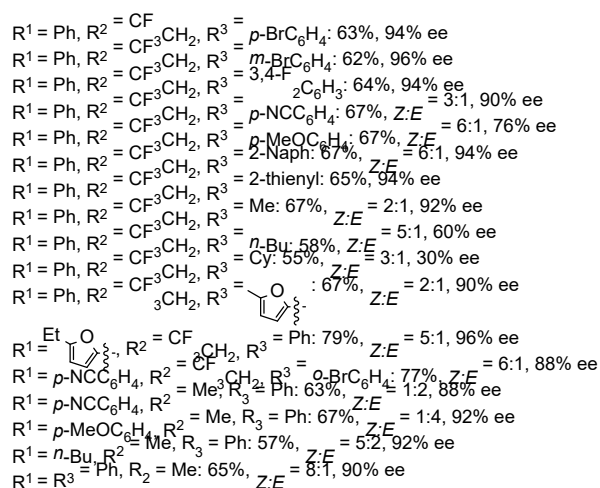
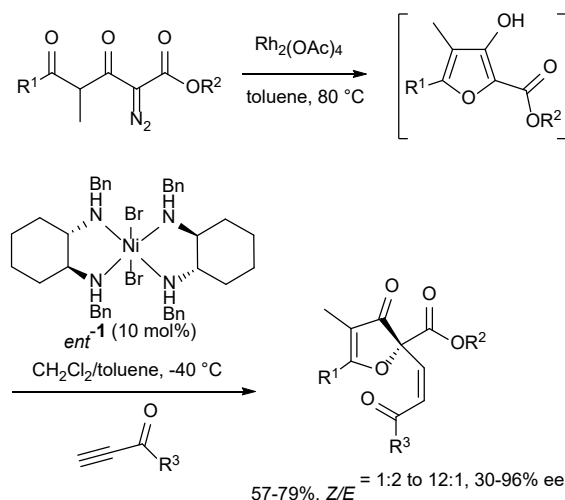
In 2017, chiral preformed nickel catalyst **1** was applied at only 2 mol% of catalyst loading by Ni et al. to promote the enantioselective Michael addition of  $\gamma,\delta$ -unsaturated  $\beta$ -ketoesters to nitrostyrenes.<sup>47</sup> This process was performed at room temperature in toluene as solvent in the presence of TEA as base. The corresponding chiral Michael adducts were not isolated but directly submitted to cyclization through a second Michael addition occurring by adding one equivalent of tetramethylguanidine (TMG) to the reaction mixture. This resulted in the formation of chiral multifunctionalized cyclohexenol derivatives exhibiting three contiguous stereocenters in moderate to excellent yields (33-96%), moderate diastereoselectivities (34-66% de) and generally high ee values (26-94% ee), as shown in Scheme 24. Indeed, in almost all cases of substrates the tandem double Michael reaction proceeded with high enantioselectivities (86-94% ee) excepted for a nitroolefin bearing an electron-withdrawing substituent (Ar = *p*-NCC<sub>6</sub>H<sub>4</sub>) which produced the desired product with only 26% ee.



**Scheme 24** Tandem double Michael reaction of nitrostyrenes with  $\gamma,\delta$ -unsaturated  $\beta$ -ketoesters.

In 2018, Svenda et al. investigated diverse enantioselective nickel-catalyzed Michael additions of 2-alkoxycarbonyl-3(2H)-furanones in situ generated from rhodium(II)-catalyzed cyclization of stable  $\alpha$ -diazo carbonyl precursors in toluene at 80 °C in the presence of Rh<sub>2</sub>(OAc)<sub>4</sub> (Scheme 25).<sup>48</sup> These substituted 2-alkoxycarbonyl-3(2H)-furanones were added at -40 °C to terminal alkynones as Michael acceptors in the presence of 10 mol% of chiral preformed nickel catalyst *ent*-**1** in a mixture of dichloromethane and toluene as solvent. The Michael addition afforded the corresponding chiral highly functionalized products with good yields (57-79%) preferentially as the *Z*-diastereomers obtained with moderate to excellent enantioselectivities (30-96% ee). In spite of preferential formation of the *Z*-diastereomers in most cases, the *Z* configuration was found labile and, consequently, the reported *Z/E* ratios may not accurately reflect the inherent diastereoselectivity of the reaction. Generally, (hetero)aryl alkynyl ketones reacted with better enantioselectivities than alkyl alkynyl ketones.

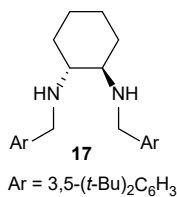
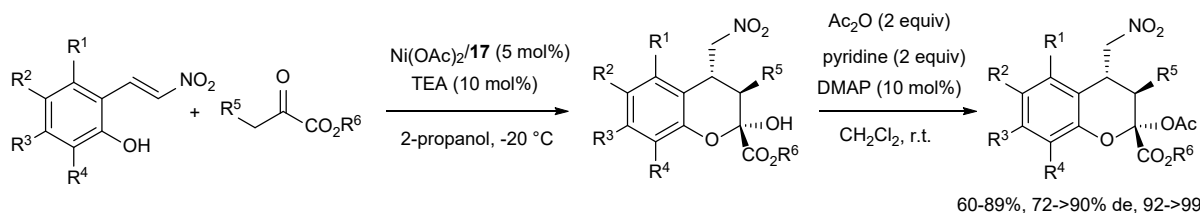
These tandem cyclization/Michael reactions allowed the synthesis of highly functionalized chiral products featuring a quaternary stereocenter at the 3(2H)-furanone ring that could be potentially active molecules in medicinal chemistry. One limitation of this methodology was the limited scope of the Michael acceptors since the obtention of lower enantioselectivities (30-60% ee) with alkyl alkynyl ketones ( $R^3 = \text{Cy}, n\text{-Bu}$ ) were observed with the exception of methyl alkynyl ketone ( $R^3 = \text{Me}$ ) which reacted with 92% ee.



**Scheme 25** Tandem cyclization/Michael reaction of terminal alkynones with  $\alpha$ -diazo carbonyl precursors.

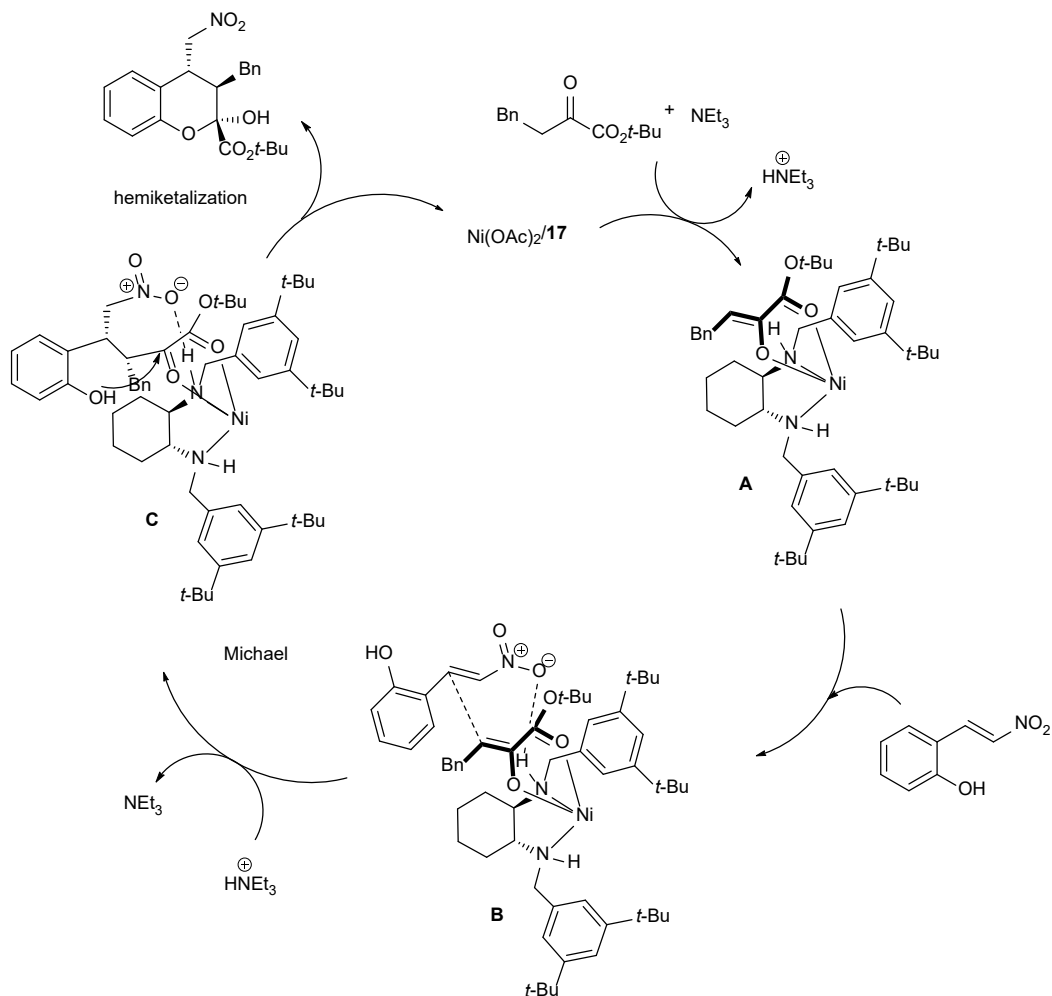
In 2019, Deng and Yang reported an enantioselective nickel-catalyzed domino Michael/hemiacetalization reaction of  $\alpha$ -ketoesters with 2-(2-nitrovinyl) phenols, providing after subsequent acetalization an easy access to a wide range of structurally diverse polysubstituted chiral chromanes in good yields (60-89%), generally excellent diastereoselectivities (72->90% de) combined with uniformly excellent enantioselectivities (92->99% ee), as illustrated in Scheme 26.<sup>49</sup> The domino process was performed at -20 °C in isopropanol as solvent in the presence of 5 mol% of a preformed catalyst derived from chiral 1,2-diamine ligand **17**. Actually, all the substrates reacted with >88% de excepted sterically hindered ones ( $R^4 = \text{Cl}, R^5 = t\text{-BuCH}_2$ ) which led to the corresponding products with 71-75% de. To explain the stereoselectivity of the reaction, the authors proposed the mechanism depicted in Scheme 26, beginning with the activation of the  $\alpha$ -ketoester by the chiral nickel catalyst through the formation of Ni(II)-enolate intermediate **A**. Because of the hydrogen-bonding interactions between the NH of the ligand and the nitro group of the nitroalkene, the latter approached intermediate **A** from the *Re* face (C=C) in transition state **B**, thus forming intermediate **C**. Subsequently, the phenol hydroxyl attacked the carbonyl group

from the *Si* face (C=O) due to the steric hindrance between the benzyl and nitro groups, which formed chromanol. Finally, the latter was directly acetylated to afford the product.



- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 73%, >90% de, 96% ee
- R<sup>1</sup> = OMe, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 73%, >90% de, 96% ee
- R<sup>1</sup> = F, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 81%, >90% de, 92% ee
- R<sup>1</sup> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>2</sub> = Me, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 75%, >90% de, 95% ee
- R<sup>1</sup> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>2</sub> = Cl, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 71%, >90% de, 94% ee
- R<sup>1</sup> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>2</sub> = Br, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 70%, >90% de, 94% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>4</sub> = H, R<sub>3</sub> = OMe, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 84%, >90% de, 96% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>4</sub> = H, R<sub>3</sub> = Cl, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 70%, >90% de, 95% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = H, R<sub>4</sub> = Cl, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu: 62%, 75% de, >99% ee
- R<sup>1</sup>, R<sup>2</sup> = (CH=CH), R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = *p*-ClC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, R<sub>6</sub> = t-Bu: 67%, >90% de, 98% ee
- R<sup>1</sup>, R<sup>2</sup> = N=CH-CH=CH, R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = *p*-ClC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, R<sub>6</sub> = t-Bu: 68%, >90% de, 95% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, R<sub>6</sub> = t-Bu: 84%, >90% de, 98% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = *p*-ClC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, R<sub>6</sub> = t-Bu: 74%, >90% de, 96% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Me, R<sub>6</sub> = t-Bu: 66%, >90% de, 96% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = *n*-Pr, R<sub>6</sub> = t-Bu: 78%, >90% de, 95% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = *t*-BuCH<sub>2</sub>, R<sub>6</sub> = t-Bu: 69%, 72% de, 95% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = MeO(CH<sub>2</sub>)<sub>2</sub>, R<sub>6</sub> = t-Bu: 72%, 90% de, >99% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = allyl, R<sub>6</sub> = t-Bu: 79%, >90% de, 97% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Cy, R<sub>6</sub> = t-Bu: 61%, >90% de, 97% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Bn, R<sub>6</sub> = Et: 73%, >90% de, 95% ee
- R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Bn, R<sub>6</sub> = Me: 60%, >90% de, 92% ee

mechanism (with R<sup>1</sup> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H, R<sub>5</sub> = Bn, R<sub>6</sub> = t-Bu):



**Scheme 26** Domino Michael/hemiacetalization reaction of 2-(2-nitrovinyl) phenols with  $\alpha$ -ketoesters followed by acetalization.

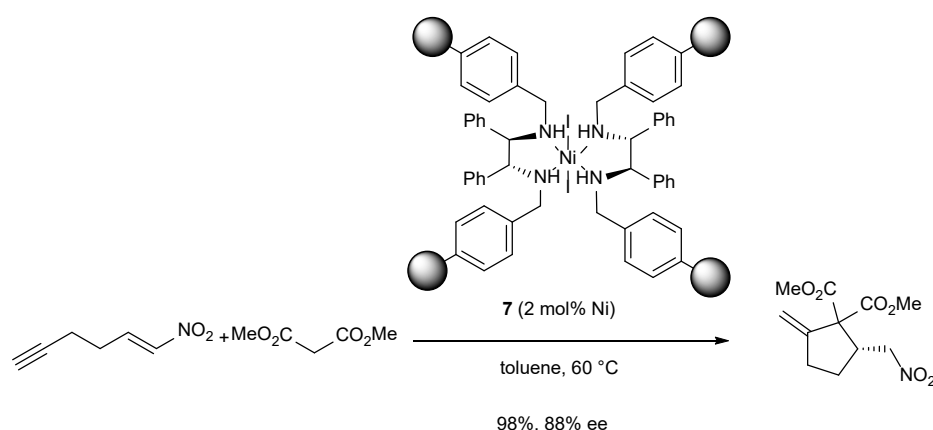
In 2020, Feng et al. developed enantioselective nickel-catalyzed domino Michael/cyclization/Schmidt-type rearrangement/imidization reaction between vinyl azides and (*E*)-alkenyloxindoles (Scheme 27).<sup>50</sup> Promoted at 30 °C in dichloromethane as solvent by 10 mol% of a chiral catalyst in situ generated from Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and *N,N'*-dioxide ligand **18**, it afforded a wide variety of chiral 3,2'-pyrrolinyl spirooxindoles with high yields (80-95%) and generally both high diastereo- (66->90% de) and enantioselectivities (80-98% ee). Both  $\alpha$ -aliphatic and  $\alpha$ -(hetero)aromatic substituted vinyl azides were compatible. Various (*E*)-alkenyloxindoles bearing different ester groups (R<sup>1</sup>) reacted smoothly to give the corresponding products with high yields (90-95%) and stereoselectivities (>90% de, 85-92% ee) with the ee values slightly decreased in the case of less steric hindered ester groups. Moreover, the presence of different types of substituents on the phenyl ring of the (*E*)-alkenyloxindoles was well tolerated regardless of their electronic nature or position. Notably, almost a single diastereomer was obtained in all cases of substrates (>90% de) with the exception of 3-thienyl-substituted vinyl azide (R<sup>3</sup> = 3-thienyl) which delivered a product with only 66% de. The mechanism of the domino reaction involved asymmetric 1,4-conjugate addition of the vinyl azide to the (*E*)-alkenyloxindole to give intermediate **A** which subsequently cyclized into intermediate **B**. Then, the latter underwent a Schmidt-type rearrangement to form intermediate **C** which finally delivered the desired product through imidization.





**Scheme 27** Domino Michael/cyclization/Schmidt-type rearrangement/imidization reaction of (*E*)-alkenyloxindoles with vinyl azides.

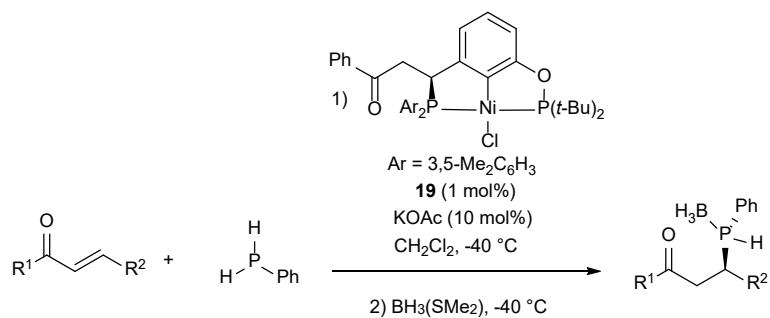
In the same year, Kramer and Kegnaes described an unprecedented enantioselective nickel-catalyzed domino Michael/Conia-ene reaction between a  $\beta$ -nitroalkene bearing a pendant alkyne and dimethyl malonate (Scheme 28).<sup>26</sup> This formal [4+1] annulation afforded in toluene at 60 °C the corresponding chiral functionalized *exo*-methylenecyclopentane with both high yield (98%) and enantioselectivity (88% ee) by using heterogeneous chiral catalyst **7** arisen from copolymerization of the corresponding vinyl-functionalized nickel(II)-bisdiamine complexes. The scope of this methodology remained limited to only one substrate.



**Scheme 28** Domino Michael/Conia-ene reaction of a  $\beta$ -nitroalkene bearing a pendant alkyne with dimethyl malonate.

In 2021, Duan and Wang reported the first highly enantioselective catalytic synthesis of *P*-stereogenic secondary phosphine-boranes.<sup>51</sup> This methodology was based on the asymmetric phospho-Michael addition of a primary phosphine, such as phenylphosphine, to  $\alpha,\beta$ -unsaturated ketones upon catalysis with only 1 mol% of newly designed chiral bisphosphine pincer-nickel complex **19**. Performed in dichloromethane as solvent at -40 °C, the reaction afforded after subsequent  $\text{BH}_3$  protection with  $\text{BH}_3\text{-SMe}_2$ , a variety of *P*-stereogenic secondary phosphine-boranes with both moderate to high yields (57-92%) and diastereoselectivities (50->90% de) combined with good to excellent enantioselectivities (77-99% ee), as presented in Scheme 29. A range of  $\alpha,\beta$ -unsaturated ketones with various functional groups were compatible. For example, either electron-withdrawing or electron-donating groups at the *para*-position of the phenyl ring of  $\beta$ -aryl  $\alpha,\beta$ -unsaturated phenyl ketones were well tolerated, leading to the desired products with high enantio- and diastereoselectivities (94-95% ee and 82->90% de, respectively). When substituents were present at the *ortho*- or *meta*-position of the phenyl ring ( $\text{R}^2$ ) of  $\beta$ -aryl  $\alpha,\beta$ -unsaturated phenyl ketones, the reaction of these substrates also proceeded with comparable excellent ee values (94-97% ee) albeit with slightly lower de values (75->90% de).  $\beta$ -Naphthyl- and  $\beta$ -ferrocenyl-substituted  $\alpha,\beta$ -unsaturated ketones were also suitable substrates, providing the corresponding phosphine-boranes with high enantioselectivities (89-92% ee) combined with lower diastereoselectivity levels (66-84% de). Moreover, different  $\beta$ -heteroaryl-substituted  $\alpha,\beta$ -unsaturated ketones ( $\text{R}^2 = 2\text{-furyl}, 2\text{-thienyl}, 2\text{-pyridyl}$ ) which could bind to the nickel center through the heteroatom, led to the products with moderate to good stereocontrol (50-87% de, 88-95% ee). Furthermore,  $\beta$ -alkyl-substituted  $\alpha,\beta$ -unsaturated ketones also underwent the tandem reaction with moderate to high de values (50-87% de) and high enantioselectivities (88-95% ee). The formed *P*-stereogenic secondary phosphines constituted useful precursors for the synthesis of other phosphorus compounds to be employed as chiral phosphine ligands. A mechanism depicted in Scheme 29 was proposed by the authors, beginning with the formation of PCP'-Ni-OAc complex **A** through anion exchange from the chiral catalyst. Then, transphosphination occurred between  $\text{H}_2\text{PPh}$  and **A**, leading to nickel phosphide intermediate **B**. Subsequently, the nucleophilic phosphorus addition to the  $\beta$ -position of the  $\alpha,\beta$ -unsaturated

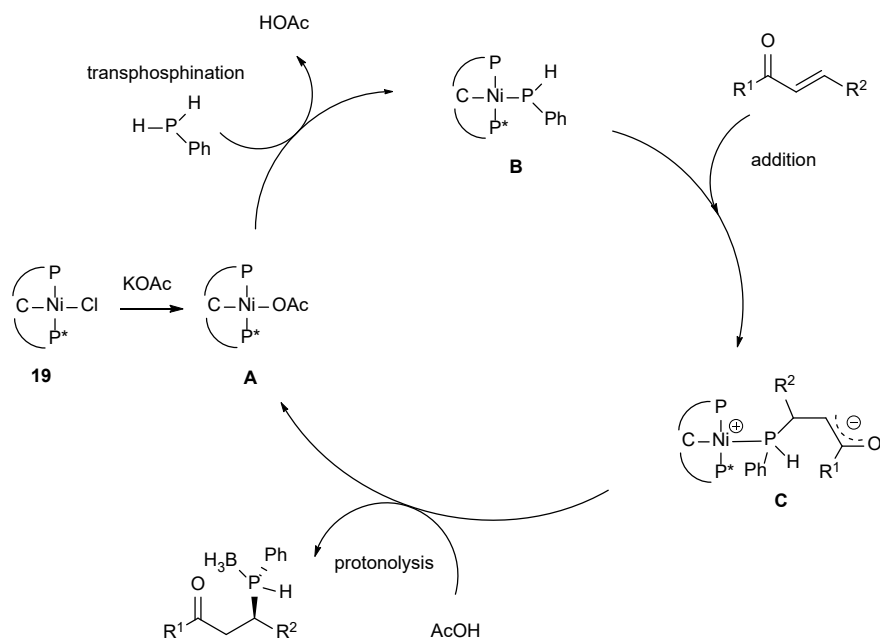
ketone generated nickel phosphine complex **C** exhibiting a pendant anion. Finally, the reaction of nickel intermediate **C** with HOAc delivered the product along with regenerated active catalyst **A**.



57-92%, 50->90% de, 77-99% ee

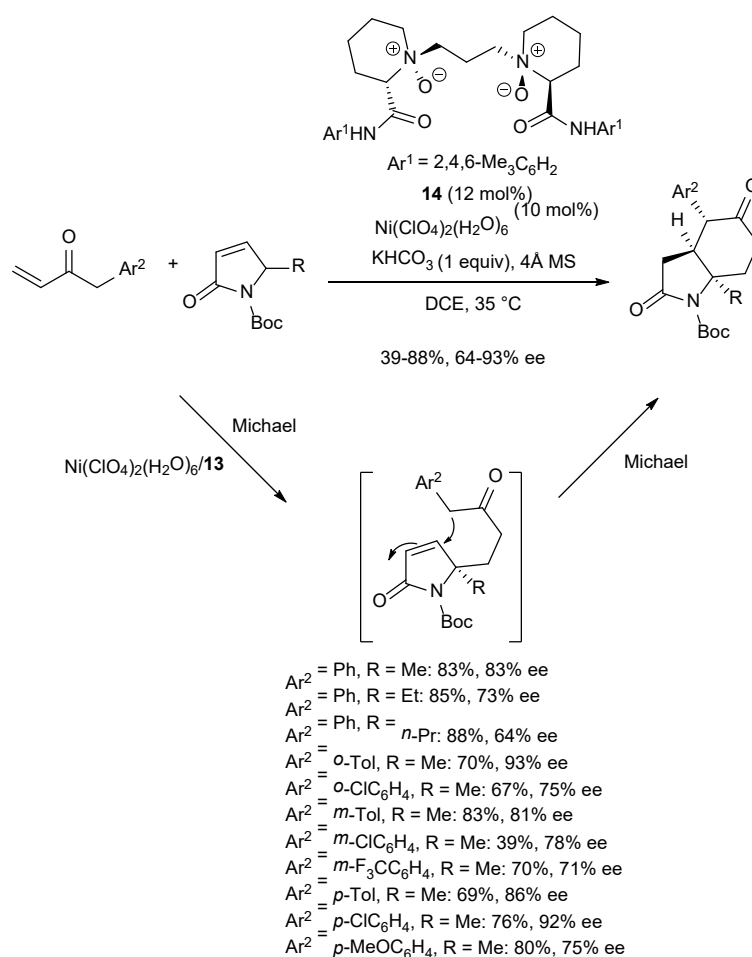
R<sup>1</sup> = R<sup>2</sup> = Ph: 80%, 86% de, 94% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *p*-FC<sub>6</sub>H<sub>4</sub>: 87%, 82% de, 94% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *p*-ClC<sub>6</sub>H<sub>4</sub>: 81%, 86% de, 95% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *p*-BrC<sub>6</sub>H<sub>4</sub>: 85%, 90% de, 95% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *p*-Tol: 87%, 90% de, 94% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>: 83%, 90% de, 94% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *o*-MeOC<sub>6</sub>H<sub>4</sub>: 76%, 75% de, 97% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *m*-MeOC<sub>6</sub>H<sub>4</sub>: 84%, 90% de, 94% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = 2-Naph: 80%, 84% de, 92% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = ferrocenyl: 91%, 66% de, 89% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = 2-furyl: 89%, 86% de, 94% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = 2-thienyl: 87%, 86% de, 93% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *i*-Pr: 77%, 78% de, 88% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *c*-Pr: 87%, 78% de, 77% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = Cy: 88%, 80% de, 89% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = Boc-N<img alt="piperidine ring" data-bbox="510 460 530 475"/>: 76%, 66% de, 93% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = Br<img alt="pyridine ring" data-bbox="510 480 530 495"/>: 57%, 50% de, 88% ee  
 R<sup>1</sup> = Ph, R<sup>2</sup> = *t*-Bu<img alt="pyridine ring" data-bbox="510 500 530 515"/>-N<img alt="phenyl ring" data-bbox="510 515 530 530"/>: 79%, 80% de, 95% ee  
 R<sup>1</sup> = <img alt="pyridine ring" data-bbox="440 525 460 540"/>-N<img alt="phenyl ring" data-bbox="440 540 460 555"/>, R<sup>2</sup> = 2-furyl: 79%, >90% de, 85% ee  
 R<sup>1</sup> = <img alt="pyridine ring" data-bbox="440 555 460 570"/>-N<img alt="phenyl ring" data-bbox="440 570 460 585"/>, R<sup>2</sup> = *p*-Tol: 86%, >90% de, 99% ee  
 R<sup>1</sup> = <img alt="pyridine ring" data-bbox="440 585 460 600"/>-N<img alt="phenyl ring" data-bbox="440 600 460 615"/>, R<sup>2</sup> = 2-Naph: 92%, >90% de, 85% ee

proposed mechanism:



**Scheme 29** Tandem phospha-Michael/borylation of  $\alpha,\beta$ -unsaturated ketones with phenylphosphine.

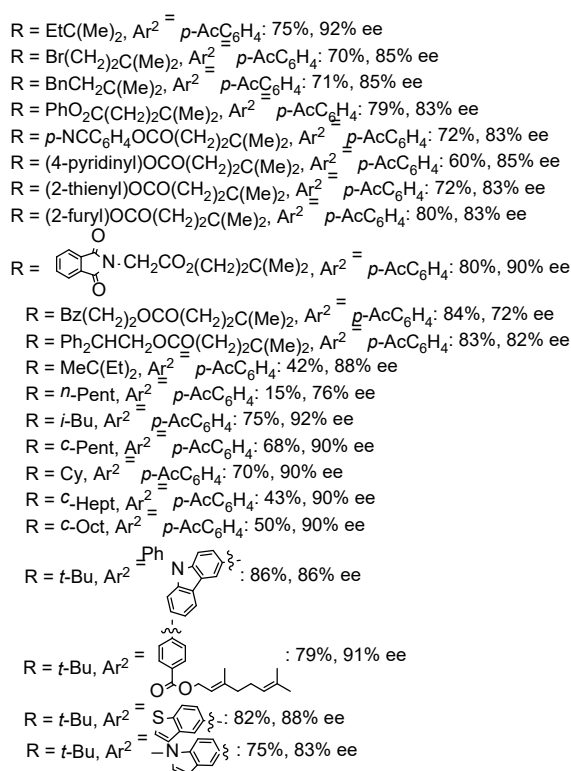
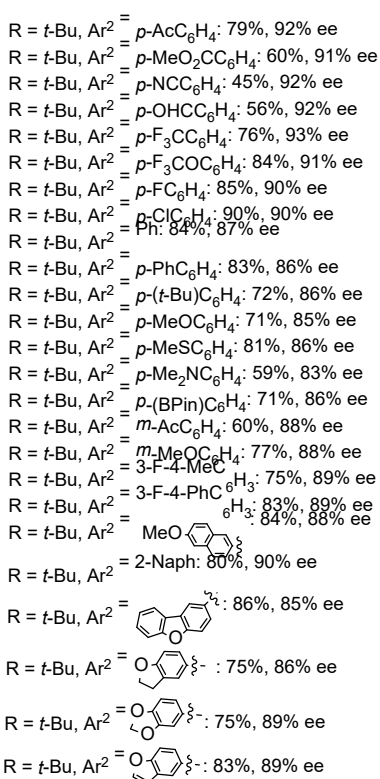
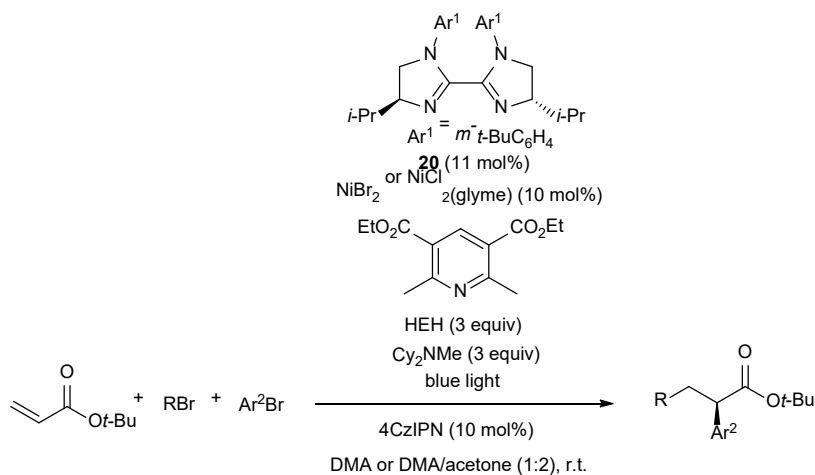
In 2022, enantioselective domino double Michael reactions between  $\gamma$ -alkyl  $\alpha,\beta$ -unsaturated butyrolactams and  $\alpha,\beta$ -unsaturated ketones, such as benzyl vinyl ketones, were developed by Wei and Xie (Scheme 30).<sup>40</sup> The one-pot process performed in DCE at 35 °C in the presence of 12 mol% of chiral *N,N'*-dioxide ligand **14** and 10 mol% of  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  allowed the synthesis of chiral octahydroindoles to be achieved as single diastereomers in both moderate to high yields (39–88%) and enantioselectivities (64–93% ee). The size of the substituent on the  $\gamma$ -carbon of the butyrolactam (*R*) was found to have an impact on the enantioselectivity of the reaction since the lowest ee value (64% ee) was observed in the reaction of a propyl-substituted substrate (*R* = *n*-Pr). Furthermore, the presence of a substituent on the phenyl ring of the benzyl vinyl ketone (*Ar*<sup>2</sup>) had a great incidence on the enantioselectivity. For example, a benzyl vinyl ketone bearing an *ortho*-methylphenyl ring provided the best ee value (93% ee), while one with an electron-withdrawing chloride at the *ortho*-position led to the corresponding product with a dramatically lower enantioselectivity (75% ee). Moreover, the presence of either electron-withdrawing or electron-donating substituents at the *meta*-position reduced the enantioselectivities (71–81% ee).



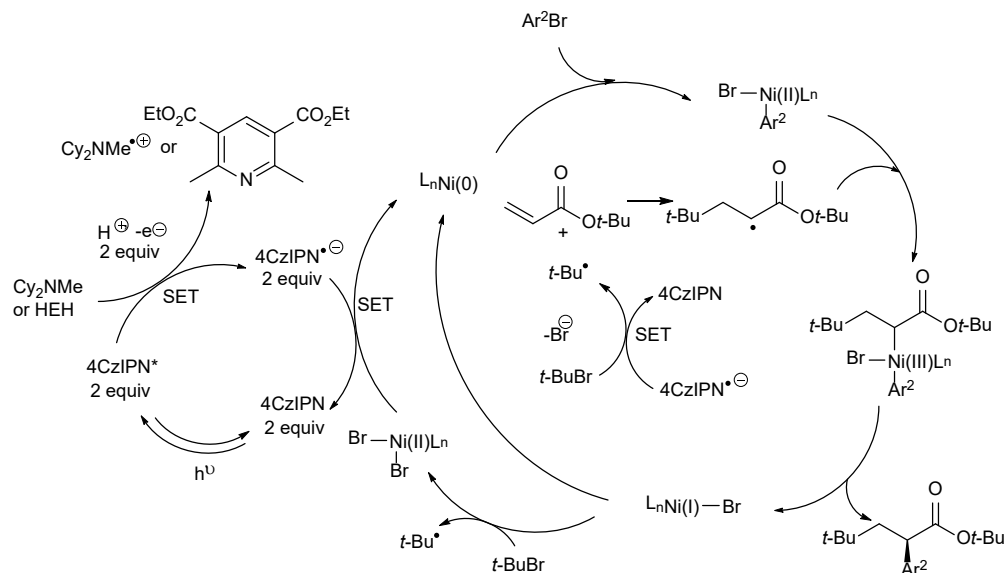
**Scheme 30** Domino double Michael reaction of benzyl vinyl ketones with  $\gamma$ -alkyl  $\alpha,\beta$ -unsaturated butyrolactams.

Nonsteroidal anti-inflammatory drugs constitute a major class of molecules in medicinal chemistry. In 2022, Walsh and Mao described a novel asymmetric route to these products based on an enantioselective three-component domino Michael/arylation reaction of *tert*-butyl acrylate with tertiary alkyl bromides and aryl bromides performed via cooperative nickel and photoredox catalysis (Scheme 31).<sup>52</sup> Indeed, in the presence of 10 mol% of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-

dicyanobenzene (4CzIPN) as photoredox catalyst combined with a chiral nickel catalyst in situ generated from 10 mol% of NiBr<sub>2</sub> or NiCl<sub>2</sub>-glyme and 11 mol% of chiral bisimidazoline (BiIM) ligand **20**, *tert*-butyl acrylate underwent at room temperature under blue LED irradiation a domino radical alkylation/arylation reaction with tertiary alkyl bromides and aryl bromides to give the corresponding chiral  $\alpha$ -aryl esters with variable yields (15-90%) and moderate to high enantioselectivities (72-93% ee). The reaction required the presence of 3 equivalents of Cy<sub>2</sub>NMe as reducing agent and the same quantity of Hantzsch ester (HEH) as terminal electron donor in *N,N*-dimethylacetamide (DMA) or a 1:2 mixture of *N,N*-dimethylacetamide and acetone as the solvent. The catalyst system tolerated a remarkably wide range of functionalized alkyl- and aryl-bromides, providing in almost all cases high ee values (83-93% ee). It must be noted that this asymmetric reductive difunctionalization of *tert*-butyl acrylate presented the advantage to avoid metal reductants by using an Hantzsch ester as organic reductant. The authors proposed the catalytic cycle depicted in Scheme 31 based on a dual nickel/photoredox catalysis. The active catalyst (BiIM)Ni(0) was generated in situ in two SET steps by the reduced photocatalyst 4CzIPN<sup>•-</sup>. The (BiIM)Ni(0) catalyst oxidatively added to the aryl bromide to give the (BiIM)Ni(Ar)Br complex. The alkyl bromide underwent SET by either the Ni or reduced 4CzIPN<sup>•-</sup> to generate an alkyl halide radical anion, which lost bromide to give a tertiary radical. Addition of this tertiary radical to the acrylate formed an  $\alpha$ -carbonyl radical that was further trapped by the (BiIM)Ni(Ar)Br complex to form the reactive Ni(III) species. Then, the latter underwent rapid reductive elimination to give the final product. In the photoredox cycle, photoexcited 4CzIPN\* reacted with HEH to afford 4CzIPN<sup>•-</sup>. Then, 4CzIPN<sup>•-</sup> was oxidized by the nickel catalyst (Ni(II)/Ni(I)) and/or the alkyl bromide to regenerate 4CzIPN.



proposed mechanism (with  $\text{R} = \text{t-Bu}$  and  $\text{L}_n = \text{BilM}$ ):



**Scheme 31** Three-component domino Michael/arylation reaction of *tert*-butyl acrylate with tertiary alkyl bromides and aryl bromides.

## 5. Conclusions

By the very fact of the lower cost of nickel in comparison with other transition metals, a range of novel chiral nickel catalysts have been designed and applied in the last few years to promote novel highly enantioselective conjugate additions of a variety of nucleophiles to many types of activated olefins. Among them, asymmetric conjugate additions of various 1,3-dicarbonyl compounds and derivatives to nitroalkenes have been successfully developed in the presence of different types of novel heterogeneous catalysts with remarkable enantioselectivities of 92–99% ee. Interestingly, these reactions were applied to the synthesis of several bioactive molecules, including adamantylated GABA analogues, blockbuster drug pregabalin, and  $\gamma$ -aminobutyric acid drugs phenibut, baclofen and rolipram. Along with 1,3-dicarbonyl compounds, a range of other nucleophiles, such as 2-acetyl azaarenes,  $\beta$ -ketophosphinates, and  $\beta$ -ketosulfones, have been added to functionalized nitroolefins, such as  $\beta$ -trifluoromethyl- $\beta$ -disubstituted nitroolefins,  $\beta$ -difluoromethyl- $\beta$ -disubstituted nitroolefins and  $\beta$ -nitroacrylates, with very high ee values (93–>99% ee). In addition, excellent enantioselectivities have been described in enantioselective Michael additions of carbon nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds and derivatives. For example, *N*-Boc-oxindoles were added to methyl vinyl ketone with 87% ee; silyl ketene imines to indol-2-ones with 98% ee, and  $\gamma$ -alkyl  $\alpha,\beta$ -unsaturated butyrolactams to  $\alpha,\beta$ -unsaturated carbonyl compounds with 84% ee. Moreover, a variety of enantioselective nickel-catalyzed domino/tandem reactions initiated by Michael additions have allowed the economic synthesis of complex molecules with uniformly excellent ee values (93–>99% ee). Although a wide variety of chiral ligands, including 1,2-diamines, bisoxazolines, *N,N'*-dioxides, bisimidazoli(d)ines, bisphosphines, bispiperidines among others, have already been successfully involved in these reactions along with remarkable heterogeneous catalysts in accordance with the concept of green chemistry, other types of chiral complexes will have to be investigated in the near future to render these transformations even more efficient, economical, convenient, and practical. The scope of the reactions will also have to be extended to other types of nucleophiles as well as to more challenging Michael acceptors, such as aldehydes and extended Michael acceptors. The improvement of the diastereoselectivity in the formation of products exhibiting two or more stereocenters is also expected. In spite of the remarkable developments reported so far, other challenges remain, such as the application of these reactions to the total synthesis of important bioactive and natural products.

## Conflict of interest

The author confirms that this article content has no conflict of interest.

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