

# 1

## Copper-Catalyzed Coupling for a Green Process

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### 1.1 Introduction

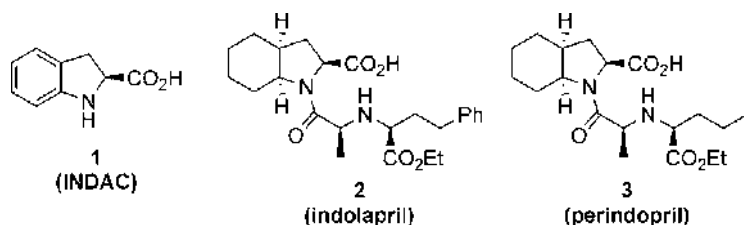
Modern processes are trending toward green and sustainable chemistries. The incorporation of catalysis in synthesis is one of the principles of green chemistry [1]; the use of a stoichiometric reagent can then be avoided and the result of this substitution is often a reduction of cost. This chapter illustrates these concepts with a Cu-catalyzed cyclization reaction.

When looking at routes to new targets, or a new route to an old target, luck can play an important role. Familiar technology helps not only in the planning stage but also in the implementation of the process, as timelines can be reduced with little or no learning curve. An understanding of the technology reduces the risk of failure, especially if a large number of examples are known. Of course, the luck element can be reduced if many technologies are accessible, as too many choices can make the selection of a specific process difficult [2].

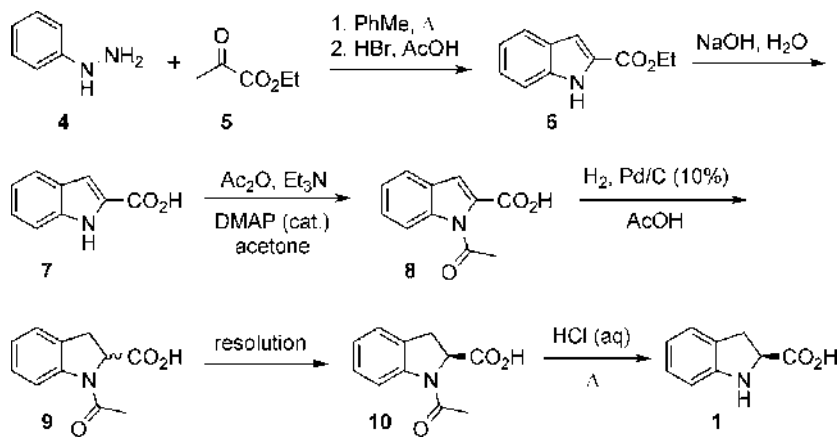
The general concepts for route selection were applied to the synthesis of (*S*)-2-indoline carboxylic acid (**1**), commonly called INDAC (Figure 1.1). This compound is a component of angiotensin 1-converting enzyme (ACE) inhibitors indolapril (**2**) and perindopril (**3**).

A new process was required, as the existing manufacturing route had seven steps and involved a classic resolution with a maximum yield of 50% for this step (Scheme 1.1) [3–6]. The approach was based on a Fisher indole synthesis. To achieve an efficient resolution, some functional group modifications were required that added steps to the synthesis. For example, the indole synthesis gives the ethyl ester **6** that has to be hydrolyzed, while the nitrogen has to be acylated to stop it from interfering in the resolution.

To increase the efficiency of the synthesis, a number of different strategies can be envisioned for construction of the indole and the chiral center. Indeed, other approaches had already been reported as well as different variations of the route shown in Scheme 1.1. These include classical resolution of the acid **1** [7–11] and enzymatic resolutions of esters derived from **1** [4,12–15]. Another approach uses a ring closure to prepare the five-membered ring in



**Figure 1.1** Structures of INDAC (1) and ACE inhibitors indolapril (2) and perindopril (3).

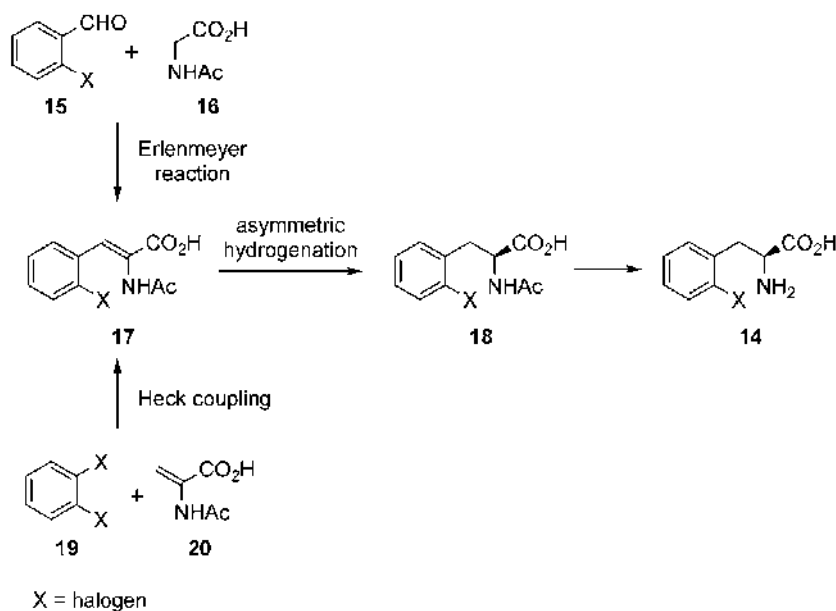
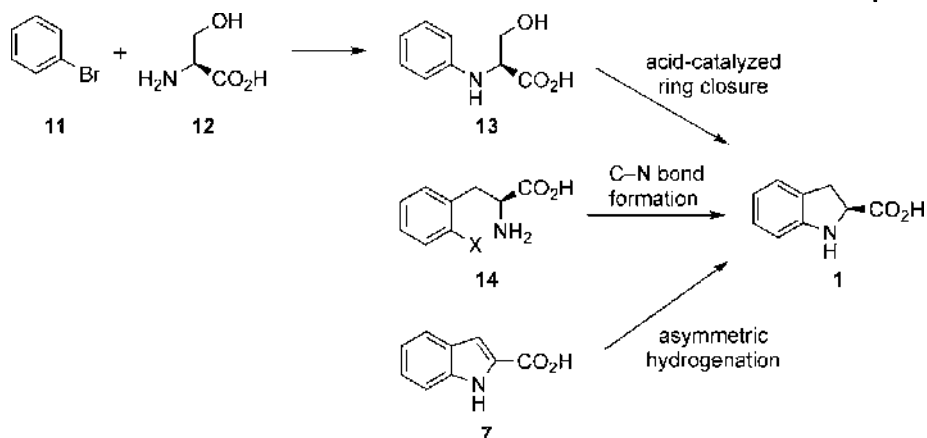


**Scheme 1.1** Resolution-based synthesis of INDAC (1).

which an aniline displaces an  $\alpha$ -chlorocarboxylic acid, in turn derived from an asymmetric reduction of the corresponding  $\alpha$ -keto acid with sodium borohydride in the presence of D-proline [16]. The use of a chiral base to perform a kinetic resolution by acylation of a 2-substituted indole has also been reported [17].

Some of the possible retrosynthetic disconnections are shown in Figure 1.2 [18]. In addition, a number of enzyme-based approaches can be used to access the intermediate amino acid **14** (Figure 1.3). The formation of the aryl–nitrogen bond is strategic in a number of these routes, and some of the approaches require that the stereochemical integrity of the amine functionality is retained during the *N*-arylation step. Other work on the preparation of arylamines suggested that formation of the C–N bond was a viable option, with a number of potential routes to the amino acid precursor **14** also being available [19].

A rapid entry to INDAC (**1**) would be to prepare the corresponding indole and then perform an asymmetric reduction. The hydrogenation of 2-substituted indoles has been achieved with Rh in the presence of (*R,R*)-2,2''-bis[(*S*)-1-(diphenylphosphino)ethyl]-1,1''-biferrocene ((*S,S*)-(*R,R*)-Ph-TRAP, **26**)



**Figure 1.2** Representative examples for the retrosynthetic analysis of INDAC (1).

and  $\text{Cs}_2\text{CO}_3$  [20]. A 95% yield in 95% ee (by HPLC) was achieved with the ester 24 (Figure 1.4) in IPA, at 60 °C and 500 bar  $\text{H}_2$ , but the substrate/catalyst ratio was 100:1, which is not an economical proposition at scale [21]. In an effort to reduce the cost of the ligand, (*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta [2,1-*a*;3,4-*a'*]dinaphthalen-4-yl)piperidine ((*S*)-PipPhos, 27) was found to be effective in a Rh catalyst in  $\text{CH}_2\text{Cl}_2$  at 40 °C and 25 bar  $\text{H}_2$ , but  $\text{Cs}_2\text{CO}_3$  was still required and the ee of the product 25 was only 74% [22].

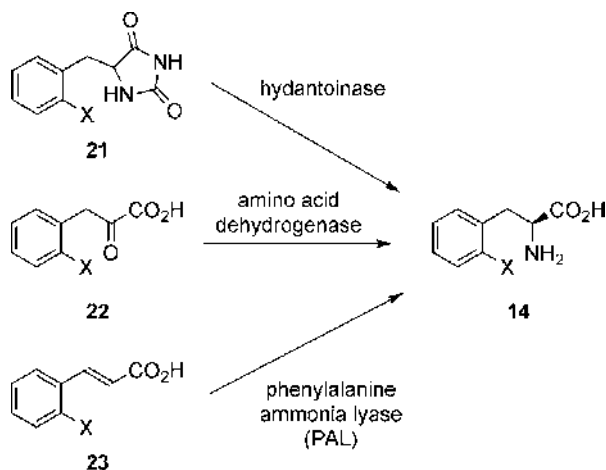


Figure 1.3 Enzyme-based approaches for the preparation of the amino acid **14**.

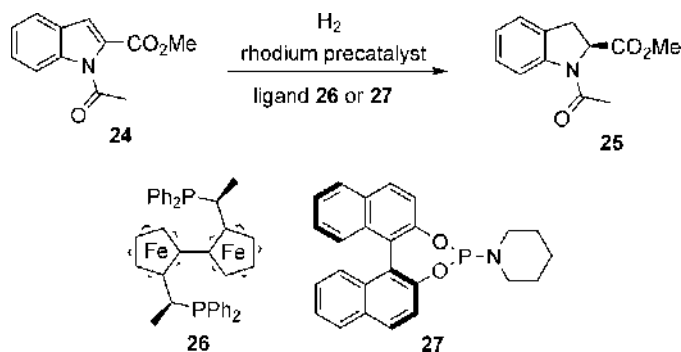


Figure 1.4 Asymmetric hydrogenation catalysts and structures of substrate and product.

## 1.2 Synthesis of Amino Acid **14**

Again, Figures 1.2 and 1.3 illustrate a variety of approaches to the amino acid **14** or a simple derivative. Each approach has its advantages and disadvantages and, for the current application, must be amenable to performing at scale [23,24].

### 1.2.1 Asymmetric Hydrogenation Approach

There are numerous catalyst and ligand systems available to prepare  $\alpha$ -amino acids and derivatives from enamide **17** [25]. Our in-house experience using monodentate phosphoramidites such as **27** (Figure 1.4) and the low cost of these ligands led us to pursue catalysts based on this class of ligands [26–28].

The enamide substrate **17** for the asymmetric hydrogenation can be prepared by an Erlenmeyer or azlactone synthesis (Figure 1.2). This has been used at scale in the preparation of a number of unnatural amino acids [29–31]. The starting material for this is the aldehyde **15**. However, the yield of the enamide is usually good rather than excellent. The alternative approach to **17** employs a Heck coupling with the appropriate dehydroalanine **20** (Figure 1.2) [32]. Although Pd is used, the catalyst loading can be reduced to a very small amount so that it is not a major cost contributor to the overall sequence and a ligand is not required [33,34]. The other component for the Heck method is a 1,2-dihalobenzene **19**.

The drawback of using an asymmetric hydrogenation is the need for an *N*-acyl group that then has to be hydrolyzed to provide the desired product **14**. This adds steps compared to the enzymatic method finally chosen. Furthermore, the cinnamic acid **23** needed for the enzymatic conversion is readily available.

Although a potential option at the planning stage, the use of serine (**12**) as the source of chirality (Figure 1.2) was not the subject of an in-depth laboratory study. Competing reactions during the cyclization of **13**, such as the elimination of water to form a dehydroalanine derivative, were seen as potential problems.

### 1.2.2

#### Enzymatic Approaches

Three enzymatic methods are outlined in Figure 1.3. In addition, there are a number of other alternatives, such as the use of an amidase to hydrolyze an *N*-acyl group from just one enantiomer of the amino acid. The undesired isomer can be racemized and submitted to the same reaction to increase the overall yield [23,24], and a second enzyme, a racemase, can be introduced to effect the interconversion of the enantiomers in the reaction vessel. The use of a hydantoinase can circumvent this recycle problem as the epimerization can be performed *in situ*. The hydantoin **21** is obtained by reaction of a phenylacetaldehyde with cyanide and ammonium carbonate (the Bucherer–Bergs reaction [35]). Phenylacetaldehyde derivatives, however, are not as readily available as benzaldehyde derivatives. In addition, phenylacetaldehydes are not particularly stable compounds, which results in low yields during their synthesis as well as in subsequent reactions.

A similar problem exists for the use of an amino acid dehydrogenase; the required  $\alpha$ -keto acids **22** are often difficult to access. In addition, these reactions to give the amino acids are in equilibria with a constant of  $\sim 1$ , so an appropriate amino donor needs to be used to allow the by-product to be removed and drive the reaction to completion [36].

In contrast, the phenylalanine ammonia lyase (PAL) uses a cinnamic acid **23** as the substrate and it is available by a number of methods all employing cheap starting materials [37]. This method became the one of choice to prepare the amino acid **14** [18].

### 1.3 Copper-Catalyzed Cyclization

The key step was the cyclization of the amino acid **14** to the desired product **1**. Some experience had already been obtained for the preparation of anilines from aryl halides (see below).

#### 1.3.1 C–N Bond Formation

The traditional reaction for the conversion of an aryl halide and amines to anilines in the presence of a stoichiometric Cu catalyst at high temperature is the Ullmann reaction [38–42]. The harsh conditions of the Ullmann reaction led to the use of Pd-catalyzed reactions for the coupling of an aryl halide with an amine to form an aniline or *N*-aryl product [43–45]. One of the major drawbacks of Pd is the price of this metal. As a consequence, applications of catalytic Cu have been investigated and found to be effective for the preparation of *N*-aryl bonds [40,46–55]. Recent advances have been made that employ a variety of ligands, which allow the amount of Cu to be reduced and lower temperatures used [56,57].

The majority of the work in this area has used aryl iodides, a class of compounds that is more expensive than the corresponding bromides or chlorides. With the less reactive aryl bromides, the expensive base Cs<sub>2</sub>CO<sub>3</sub> is typically required, and the results are often inferior to those seen in the iodide series [58–66] unless the amine is primary [67–69]. However, the use of diphenyl pyrrolidine-2-phosphonate does provide good yields for reaction between secondary amines and aryl bromides [70]. The use of Cu<sub>2</sub>O has been found to be effective for the *N*-arylation of a number of simple amides and amines even with aryl chlorides [71], while ionic organic bases, such as tetraalkylammonium and tetraalkylphosphonium carboxylates, have also been advocated with CuI [72].

As *N*-arylation is a common reaction, we needed to find conditions to allow the use of an aryl bromide or chloride as the substrate (Figure 1.5 and Table 1.1) [73,74]. The initial results with acetylacetone (**28a**) were not very successful. However, moving to the more lipophilic 2,2',6,6'-tetramethylheptane-2,5-dione (TMHD, **28b**) gave reasonable yields with aryl bromides (entries 1–5). TMHD had been used for Cu-catalyzed aromatic etherifications [75].

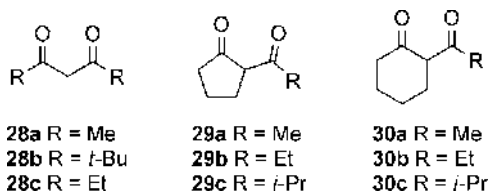


Figure 1.5 Ligands investigated for the copper *N*-arylation reaction.

**Table 1.1** Copper-catalyzed amination reactions with 1.3–1.5 equiv amine, 25 mol% ligand, and 1 M concentration of aryl halide (unless otherwise noted) [73].

Entry	Ar–X	Amine	Ligand	Base	Temperature (°C)	Time (h)	Yield (%) <sup>a)</sup>
1	C <sub>6</sub> H <sub>5</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28b</b>	Cs <sub>2</sub> CO <sub>3</sub>	120	10	86
2	4-MeOC <sub>6</sub> H <sub>4</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28b</b>	Cs <sub>2</sub> CO <sub>3</sub>	120	10	81
3	3,5-(Me) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28b</b>	Cs <sub>2</sub> CO <sub>3</sub>	120	10	84
4	4-C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28b</b>	Cs <sub>2</sub> CO <sub>3</sub>	120	10	78
5	C <sub>6</sub> H <sub>5</sub> Br	<i>n</i> -C <sub>6</sub> H <sub>13</sub> NH <sub>2</sub>	<b>28b</b>	Cs <sub>2</sub> CO <sub>3</sub>	120	10	78
6	2-MeOC <sub>6</sub> H <sub>4</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28b</b>	Cs <sub>2</sub> CO <sub>3</sub>	120	10	11
7	C <sub>6</sub> H <sub>5</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28a</b>	Cs <sub>2</sub> CO <sub>3</sub>	130	18	41
8	C <sub>6</sub> H <sub>5</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28a</b>	Cs <sub>2</sub> CO <sub>3</sub>	130	18	46 <sup>b)</sup>
9	C <sub>6</sub> H <sub>5</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28a</b>	K <sub>2</sub> CO <sub>3</sub>	130	18	43
10	C <sub>6</sub> H <sub>5</sub> Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>28a</b>	K <sub>2</sub> CO <sub>3</sub>	130	18	90 <sup>b)</sup>
11	C <sub>6</sub> H <sub>5</sub> Br	Imidazole	<b>28a</b>	K <sub>2</sub> CO <sub>3</sub>	130	18	89
12	C <sub>6</sub> H <sub>5</sub> Br	Imidazole	<b>28a</b>	K <sub>2</sub> CO <sub>3</sub>	130	18	99 <sup>b)</sup>
13	2-MeOC <sub>6</sub> H <sub>4</sub> Br	Piperidine	<b>28a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	31
14	C <sub>6</sub> H <sub>5</sub> Br	Piperidine	<b>29a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	40
15	4-MeOC <sub>6</sub> H <sub>4</sub> Br	Piperidine	<b>29a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	40
16	C <sub>6</sub> H <sub>5</sub> Br	Piperidine	<b>30a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	95 <sup>b)</sup>
17	C <sub>6</sub> H <sub>5</sub> Br	Piperidine	<b>30c</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	95 <sup>b)</sup>
18	4-MeOC <sub>6</sub> H <sub>4</sub> Br	Piperidine	<b>30a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	85 <sup>b)</sup>
19	4-MeOC <sub>6</sub> H <sub>4</sub> Br	Piperidine	<b>30c</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	85 <sup>b)</sup>
20	2-MeOC <sub>6</sub> H <sub>4</sub> Br	Piperidine	<b>30b</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	36
21	C <sub>6</sub> H <sub>5</sub> Br	Morpholine	<b>30a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	65 <sup>c)</sup>
22	C <sub>6</sub> H <sub>5</sub> Br	Morpholine	<b>30c</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	50 <sup>b)</sup>
23	C <sub>6</sub> H <sub>5</sub> Br	<i>N</i> -Me-piperazine	<b>30a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	88 <sup>c)</sup>
24	C <sub>6</sub> H <sub>5</sub> Br	Aniline	<b>30a</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	80 <sup>b)</sup>
25	C <sub>6</sub> H <sub>5</sub> Cl	Piperidine	<b>30c</b>	K <sub>2</sub> CO <sub>3</sub>	130	16	5 <sup>b)</sup>

a) Yields by GC.

b) 5 M concentration.

c) 5 M concentration and 2 equiv of amine.

High-throughput experimentation (HTE) was used to screen the many reaction parameters [76]. We found that the source of the copper was not important and both Cu(I) and Cu(II) salts gave similar results. When moving from Cs<sub>2</sub>CO<sub>3</sub> to K<sub>2</sub>CO<sub>3</sub> to reduce the cost of the base, we observed that more concentrated reactions gave higher yields (Table 1.1, entries 9–12). (This is where luck played a role.) In addition, switching to K<sub>2</sub>CO<sub>3</sub> allowed us to use the inexpensive ligand **28a** with better results (entry 10). This concentration effect was also observed with heterocyclic amines, but to a lesser degree (entries 11–12). However, the reactions of aniline and secondary amines were still in need of

improvement. Thus, ligands **29a–c** and **30a–c** were also investigated and the results showed that ligands **30a–c** performed better than the other series. However, *ortho*-substituted aryl bromides and aryl chlorides did not give high yields (entries 6, 13, 20, and 25).

The studies also showed that aminations could be observed in the absence of a transition metal catalyst. These instances occurred when KO*t*-Bu was used as the base at high temperature and a benzyne mechanism could operate [77,78]. The other instances were when a strong electron-withdrawing group was *ortho* or *para* to the bromide so that an S<sub>N</sub>Ar mechanism could account for the results.

These studies showed that aryl bromides could be used in amination reactions and that the cheaper base K<sub>2</sub>CO<sub>3</sub> could replace Cs<sub>2</sub>CO<sub>3</sub> [79]. In addition, other ligands for Cu are still being developed [56], as are alternative bases [80].

### 1.3.2

#### INDAC (**1**) Synthesis

As the halogen in the amino acid substrate **14** is substituted by the amine in the key step, the displaced halide becomes waste. The screening studies, therefore, were limited to the use of Br and Cl as the halogen. Our key to success was the ability to cyclize **14** to **1** without compromising the chirality already set. Arylation of amino acids via Cu catalysis without racemization was already precedented at the time of our study [43,46], whereas racemization in the presence of Pd is well documented [81–83]. Cu-catalyzed ring closures were known with simple amines [48,84–86] for the preparation of *N*-substituted indoles [87,88].

The initial experiments were performed with β-diketone ligands (see Section 1.3.1) [73]. However, it soon became apparent that a ligand was not required for our amination to proceed, which was consistent with another study on the arylation of amino acids via Cu catalysis [46]. In these cases, the assumption is that the amino acid acts as a ligand [89].

The results of the screening studies are summarized in Table 1.2. The initial experiment with amino acid **14b** (X = Br) was run at 100 °C in NMP and **1** was formed in 93% yield with no loss of ee (entry 1). However, a longer reaction time resulted in a lower yield and racemization (entry 2). With less catalyst and a lower temperature, the reaction was essentially complete within 2 h with no loss of enantioselectivity (entry 3).

In our new INDAC (**1**) synthesis, the Cu-catalyzed cyclization follows an enzymatic method to prepare the amino acid **14**. To avoid a solvent switch, water was tried as the solvent for the Cu reaction since others have observed that *N*-arylations could be performed in this solvent [90,91]. The reaction was still fast (2 h) and the stereochemistry was retained (entry 5). Even in the absence of Cu, the desired reaction was observed (entries 6 and 7)! It must be assumed that trace amounts of metal were present in the reaction as a low loading experiment (entry 8) gave excellent results after just 5 h.



**Table 1.2** Copper-catalyzed conversion of amino acid **14a–b** to INDAC (**1**).

**14a** (X = Cl)  
**14b** (X = Br)

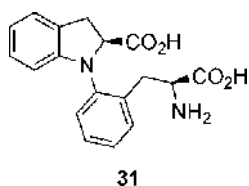
**1**

Entry	X	Solvent	CuCl (mol%)	Temperature (°C)	Time (h)	Conversion (%) <sup>a)</sup>	Yield (%) <sup>b)</sup>	ee (%) <sup>c)</sup>
1	Br	NMP	6	100	4	100	93	98.6
2	Br	NMP	6	100	26	100	79	77.6
3	Br	NMP	1	80	2	99	96	99.5
4	Br	NMP	1	80	3.5	100	94	99.6
5	Br	H <sub>2</sub> O	2	95	2	100	81	99.6
6	Br	H <sub>2</sub> O	0	95	5	37	39	—
7	Br	H <sub>2</sub> O	0	95	22	100	96	99.1
8	Br	H <sub>2</sub> O	0.01	95	5	100	95	99.5
9	Cl	H <sub>2</sub> O	0	95	19	0	0	—
10	Cl	H <sub>2</sub> O	1	95	22	40	—	—
11	Cl	H <sub>2</sub> O	1	95	40	100	88 (76)	98.3 (99.0)
12	Cl	H <sub>2</sub> O	4	95	2	100	95	99.0

- a) Conversion of starting material as determined by HPLC.  
 b) HPLC yields but those in parentheses are for isolated product.  
 c) Values in parentheses are for isolated product.

With the chloro substrate **14a** (entries 10–11), the cyclization reaction is slower, and in this case, no reaction was observed in the absence of Cu (entry 9). The use of 4 mol% of CuCl gave an excellent yield and stereochemical retention after 2 h with K<sub>2</sub>CO<sub>3</sub> as base (entry 12). The ready availability of the chloro-substituted cinnamic acid made this the substrate of choice despite the slower reaction. The copper salts were removed during the aqueous workup [19], using standard methodologies [92].

Analysis of the amination mixture showed the presence of a dimeric compound **31** that was formed by the intermolecular *N*-arylation of the product **1** with 2-chlorophenylalanine (Figure 1.6) [93].

**Figure 1.6** Structure of dimeric impurity from the Cu-catalyzed cyclization.

**Table 1.3** Sustainability comparison between old and new processes for the synthesis of INDAC (1).

Key parameters	First- versus second-generation processes (% reduction)
<i>Sustainability</i>	
Process mass intensity	32
Carbon footprint	55
Eco-indicator 99	80
<i>Economics</i>	
Manufacturing costs	Significant
Capacity	-16 <sup>a)</sup>

a) That is, an increase.

## 1.4 Sustainability

As noted in the introduction, sustainable and green chemistry is now playing an important role in synthesis design and implementation. The old synthesis comprising seven steps, which included a resolution, has now been replaced by a two-step process where the stereochemistry is set by an enzymatic reaction and no resolution is needed [93,94]. The environmental impact can be measured in a variety of ways [95–97]. A comparison of the old and new processes is summarized in Table 1.3.

The use of organic solvents was reduced significantly, as water is used as the reaction medium for both steps. Process mass intensity (PMI) is an indicator of the amount of material put into the reaction compared to the amount of desired product generated. However, water is not ignored in the PMI, which leads to only a modest reduction of this factor [98]. The carbon footprint, or life cycle analysis, takes into account the starting materials and energy that give rise to CO<sub>2</sub> emission [99], while the Eco-indicator 99 is an all-inclusive measure that covers human health, impact on the ecosystem, and resource depletion [100].

## 1.5 Summary

An improved manufacturing process to INDAC (1) was developed building on previous knowledge and expertise for the preparation of unnatural amino acids by enzymatic processes and a Cu-catalyzed *N*-arylation method. The new process has only two steps compared with the traditional route that had seven and both are run in water. In addition to cost reduction, the new process is much more sustainable illustrating that both can be achieved without compromising either. The PAL enzyme and the Cu-catalyzed cyclization are currently being used on ton scale for the preparation of INDAC (1) [18,19,101,102].

## Acknowledgments

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## References

- Anastas, P.T. and Eghbali, N. (2010) *Chem. Soc. Rev.*, **39**, 301.
- Ager, D.J. (2011) Route and process selection, in *Process Understanding: For Scale-Up and Manufacturing of Active Ingredients* (ed. I. Houson), Wiley-VCH Verlag GmbH, Weinheim, pp. 17–58.
- Hendrickx, A.J.J. and Kuilman, T. (1999) EP0937714.
- Le Goffic, F. (2006) FR2883874.
- Vincent, M., Baliarda, J., Marchand, B., and Remond, G. (1988) EP308339.
- Vincent, M., Rémond, G., Portevin, B., Serkiz, B., and Laubie, B. (1982) *Tetrahedron Lett.*, **23**, 1677.
- Buzby, G.C. (1985) US Patent 4,520,205.
- Miyata, S., Fukuda, H., and Imamura, S. (1986) EP0171616.
- Wang, Z.-X., Raheem, M.A., and Weeratunga, G. (2006) WO 2006053440.
- Chava, S., Bandari, M., and Madhuresh, K.S. (2006) WO 2006013581.
- Souvie, J.-C. and Lecouve, J.-P. (2003) EP1348684.
- Asada, M., Hamaguchi, S., Kutsuki, H., Nakamura, Y., Takashi, H., Takahara, K., Shimada, Y., Ohashi, T., and Watanabe, K. (1990) US Patent 4,898,822.
- Cho, N.R., Lim, J.H., and Kim, J.K. (2005) WO 2005051910.
- Ghisalba, O., Ramos, G., and Schaer, H.P. (1988) DE3727411.
- Asada, M., Hamaguchi, S., Nakamura, Y., Ohashi, T., and Watanabe, K. (1994) JP6296499.
- Buzby, G.C., Jr., Winkley, M.W., and McCaully, R.J. (1986) US Patent 4,614,806.
- Arp, F.O. and Fu, G.C. (2006) *J. Am. Chem. Soc.*, **128**, 14264.
- de Vries, A.H.M., de Vries, J.G., van Assema, F.B.J., de Lange, B., Mink, D., Hyett, D.J., and Maas, P.J.D. (2006) WO 2006/069799.
- de Lange, B., Hyett, D.J., Maas, P.J.D., Mink, D., van Assema, F.B.J., Sereinig, N., de Vries, A.H.M., and de Vries, J.G. (2011) *ChemCatChem*, **3**, 289.
- Kuwano, R., Sato, K., Kurokawa, T., Karube, D., and Ito, Y. (2000) *J. Am. Chem. Soc.*, **122**, 7614.
- Blaser, H.U., Spindler, F., and Studer, M. (2001) *Appl. Catal. A: Gen.*, **221**, 119.
- Mršić, N., Jerphagnon, T., Minnaard, A.J., Feringa, B.L., and de Vries, J.G. (2010) *Tetrahedron: Asymmetry*, **21**, 7.
- Ager, D.J. (2009) Synthesis of unnatural/nonproteinogenic  $\alpha$ -amino acids, in *Amino Acids, Peptides and Proteins in Organic Chemistry: Origins and Synthesis of Amino Acids*, vol. 1 (ed. A.B. Hughes), Wiley-VCH Verlag GmbH, Weinheim, pp. 495–526.
- Ager, D.J. (2008) Unnatural amino acids, in *Process Chemistry in the Pharmaceutical Industry: Challenges in an Ever Changing Climate*, vol. 2 (eds K. Gadamasetti and T. Braish), CRC Press, Boca Raton, FL, pp. 157–180.
- de Vries, J.G. and Elsevier, C.J. (eds) (2007) *The Handbook of Homogeneous Hydrogenation*, vols. 1–3 Wiley-VCH Verlag GmbH, Weinheim.
- van den Berg, M., Minnaard, A.J., Feringa, B., and de Vries, J.G. (2002) WO 0204466.
- van den Berg, M., Minnaard, A.J., Haak, R.M., Leeman, M., Schudde, E.P., Meetsma, A., Feringa, B.L., de Vries, A.H.M., Maljaars, C.E.P., Willans, C.E., Hyett, D., Boogers, J.A.F., Hendrickx, H.J.W., and de Vries, J.G. (2003) *Adv. Synth. Catal.*, **345**, 308.
- Minnaard, A.J., Feringa, B.L., Lefort, L., and de Vries, J.G. (2007) *Acc. Chem. Res.*, **40**, 1267.
- Ager, D.J., de Vries, A.H.M., and de Vries, J.G. (2012) *Chem. Soc. Rev.*, **41**, 3340.

- 30 Ager, D.J. and Laneman, S.A. (2004) The synthesis of unnatural amino acids, in *Asymmetric Catalysis on Industrial Scale* (eds H.U. Blaser and E. Schmidt), Wiley-VCH Verlag GmbH, Weinheim, pp. 259–268.
- 31 Laneman, S.A., Froen, D.E., and Ager, D.J. (1998) The preparation of amino acids via Rh(DIPAMP)-catalyzed asymmetric hydrogenation, in *Catalysis of Organic Reactions* (ed. F.E. Herkes), Marcel Dekker, New York, pp. 525–530.
- 32 Beletskaya, I.P. and Cheprakov, A.V. (2000) *Chem. Rev.*, **100**, 3009.
- 33 Willans, C.E., Mulders, J.M.C.A., de Vries, J.G., and de Vries, A.H.M. (2003) *J. Organomet. Chem.*, **687**, 494.
- 34 de Vries, A.H.M., Mulders, J.M.C.A., Mommers, J.H.M., Hendrickx, H.J.W., and de Vries, J.G. (2003) *Org. Lett.*, **5**, 3285.
- 35 Ware, E. (1950) *Chem. Rev.*, **46**, 403.
- 36 Fotheringham, I. and Taylor, P.P. (2005) Microbial pathway engineering for amino acid manufacture, in *Handbook of Chiral Fine Chemicals*, 2nd edn (ed. D.J. Ager), CRC Press/Taylor & Francis, Boca Raton, FL, pp. 31–45.
- 37 Ager, D. and de Vries, A. (2011) *Speciality Chem.*, **31**, 10.
- 38 Ullmann, F. (1903) *Ber. Dtsch. Chem. Ges.*, **36**, 2382.
- 39 Sperotto, E., van Klink, G.P.M., van Koten, G., and de Vries, J.G. (2010) *Dalton Trans.*, **39**, 10338.
- 40 Ley, S.V. and Thomas, A.W. (2003) *Angew. Chem., Int. Ed.*, **42**, 5400.
- 41 Lindley, J. (1984) *Tetrahedron*, **40**, 1433.
- 42 Beletskaya, I.P. and Cheprakov, A.V. (2004) *Coord. Chem. Rev.*, **248**, 2337.
- 43 Wolfe, J.P., Rennels, R.A., and Buchwald, S.L. (1996) *Tetrahedron*, **52**, 7525.
- 44 Buchwald, S.L., Mauger, C., Mignani, G., and Scholz, U. (2006) *Adv. Synth. Catal.*, **348**, 23.
- 45 Schlummer, B. and Scholz, U. (2004) *Adv. Synth. Catal.*, **346**, 1599.
- 46 Ma, D., Zang, Y., Yao, J., Wu, S., and Tao, F. (1998) *J. Am. Chem. Soc.*, **120**, 12459.
- 47 Kunz, K., Scholz, U., and Ganzer, D. (2003) *Synlett*, 2428.
- 48 Zhang, H., Cai, Q., and Ma, D. (2005) *J. Org. Chem.*, **70**, 5164.
- 49 Lang, F., Zewge, D., Houpis, I.N., and Volante, R.P. (2001) *Tetrahedron Lett.*, **42**, 3251.
- 50 Ma, D. and Xia, C. (2001) *Org. Lett.*, **3**, 2583.
- 51 Gujadhur, R., Venkataraman, D., and Kintigh, J.T. (2001) *Tetrahedron Lett.*, **42**, 4791.
- 52 Gujadhur, R., Bates, C.G., and Venkataraman, D. (2001) *Org. Lett.*, **3**, 4315.
- 53 Klapars, A., Antilla, J.C., Huang, X., and Buchwald, S.L. (2001) *J. Am. Chem. Soc.*, **123**, 7727.
- 54 Cristau, H.-J., Cellier, P.P., Spindler, J.-F., and Taillefer, M. (2004) *Chem. Eur. J.*, **10**, 5607.
- 55 Antilla, J.C., Klapars, A., and Buchwald, S.L. (2002) *J. Am. Chem. Soc.*, **124**, 11684.
- 56 Sperotto, E., van Klink, G.P.M., de Vries, J.G., and van Koten, G. (2010) *Tetrahedron*, **66**, 3478.
- 57 Kienle, M., Dubbaka, S.R., Brade, K., and Knochel, P. (2007) *Eur. J. Org. Chem.*, 4166.
- 58 Lu, Z., Twieg, R.J., and Huang, S.D. (2003) *Tetrahedron Lett.*, **44**, 6289.
- 59 Okano, K., Tokuyama, H., and Fukuyama, T. (2003) *Org. Lett.*, **5**, 4987.
- 60 Kelkar, A.A., Patil, N.M., and Chaudhari, R.V. (2002) *Tetrahedron Lett.*, **43**, 7143.
- 61 Lu, Z. and Twieg, R.J. (2005) *Tetrahedron Lett.*, **46**, 2997.
- 62 Kuil, M., Bekedam, E.K., Visser, G.M., van den Hoogenband, A., Terpstra, J.W., Kamer, P.C.J., van Leeuwen, P.W.N.M., and van Strijdonck, G.P.F. (2005) *Tetrahedron Lett.*, **46**, 2405.
- 63 Kwong, F.Y., Klapars, A., and Buchwald, S.L. (2002) *Org. Lett.*, **4**, 581.
- 64 Xu, L., Zhu, D., Wu, F., Wang, R., and Wan, B. (2005) *Tetrahedron*, **61**, 6553.
- 65 Yang, K., Qiu, Y., Li, Z., Wang, Z., and Jiang, S. (2011) *J. Org. Chem.*, **76**, 3151.
- 66 Wang, H., Li, Y., Sun, F., Feng, Y., Jin, K., and Wang, X. (2008) *J. Org. Chem.*, **73**, 8639.
- 67 Kwong, F.Y. and Buchwald, S.L. (2003) *Org. Lett.*, **5**, 793.
- 68 Yin, H., Jin, M., Chen, W., Chen, C., Zheng, L., Wei, P., and Han, S. (2012) *Tetrahedron Lett.*, **53**, 1265.
- 69 Liu, Z.-J., Vors, J.-P., Gesing, E.R.F., and Bolm, C. (2010) *Adv. Synth. Catal.*, **352**, 3158.

- 70 Rao, H., Fu, H., Jiang, Y., and Zhao, Y. (2005) *J. Org. Chem.*, **70**, 8107.
- 71 Xu, H. and Wolf, C. (2009) *Chem. Commun.*, 1715.
- 72 Yang, C.-T., Fu, Y., Huang, Y.-B., Yi, J., Guo, Q.-X., and Liu, L. (2009) *Angew. Chem., Int. Ed.*, **48**, 7398.
- 73 de Lange, B., Lambers-Verstappen, M.H., Schmieder-van de Vondervoort, L., Sereinig, N., de Rijk, R., de Vries, A.H.M., and de Vries, J.G. (2006) *Synlett*, 3105.
- 74 Lambers, M.M.H., de Lange, B., de Vries, A.H.M., de Vries, J.G., and Sereinig, N. (2006) WO 2006009431.
- 75 Buck, E., Song, Z.J., Tschaen, D., Dormer, P.G., Volante, R.P., and Reider, P.J. (2002) *Org. Lett.*, **4**, 1623.
- 76 de Vries, J.G. and de Vries, A.H.M. (2003) *Eur. J. Org. Chem.*, 799.
- 77 Beller, M., Breindl, C., Riermeier, T.H., and Tillack, A. (2001) *J. Org. Chem.*, **66**, 1403.
- 78 Shi, L., Wang, M., Fan, C.-A., Zhang, F.-M., and Tu, Y.-Q. (2003) *Org. Lett.*, **5**, 3515.
- 79 Shafir, A. and Buchwald, S.L. (2006) *J. Am. Chem. Soc.*, **128**, 8742.
- 80 Feng, Y.-S., Man, Q.-S., Pan, P., Pan, Z.-Q., and Xu, H.-J. (2009) *Tetrahedron Lett.*, **50**, 2585.
- 81 Parvulescu, A., De Vos, D., and Jacobs, P. (2005) *Chem. Commun.*, 5307.
- 82 Parvulescu, A.N., Jacobs, P.A., and De Vos, D.E. (2007) *Chem. Eur. J.*, **13**, 2034.
- 83 Kim, M.-J., Kim, W.-H., Han, K., Choi, Y.K., and Park, J. (2007) *Org. Lett.*, **9**, 1157.
- 84 Minatti, A. and Buchwald, S.L. (2008) *Org. Lett.*, **10**, 2721.
- 85 Guo, D., Huang, H., Zhou, Y., Xu, J., Jiang, H., Chen, K., and Liu, H. (2010) *Green Chem.*, **12**, 276.
- 86 Yang, T., Lin, C., Fu, H., Jiang, Y., and Zhao, Y. (2005) *Org. Lett.*, **7**, 4781.
- 87 Ackermann, L., Barfüßer, S., and Potukuchi, H.K. (2009) *Adv. Synth. Catal.*, **351**, 1064.
- 88 He, H.-F., Dong, S., Chen, Y., Yang, Y., Le, Y., and Bao, W. (2012) *Tetrahedron*, **68**, 3112.
- 89 Ma, D., Cai, Q., and Zhang, H. (2003) *Org. Lett.*, **5**, 2453.
- 90 Xu, H.-J., Zheng, F.-Y., Liang, Y.-F., Cai, Z.-Y., Feng, Y.-S., and Che, D.-Q. (2010) *Tetrahedron Lett.*, **51**, 669.
- 91 Zhu, X., Su, L., Huang, L., Chen, G., Wang, J., Song, H., and Wan, Y. (2009) *Eur. J. Org. Chem.*, 635.
- 92 Hwang, S.J., Cho, S.H., and Chang, S. (2008) *Pure Appl. Chem.*, **80**, 873.
- 93 Poechlauer, P., Braune, S., de Vries, A., and May, O. (2010) *Chim. Oggi/Chem. Today*, **28**, 14.
- 94 Ager, D., de Vries, A., Sereinig, N., and May, O. (2011) *Chim. Ind.*, 100.
- 95 Constable, D.J.C., Dunn, P.J., Hayler, J.D., Humphrey, G.R., Leazer, J.L., Jr., Linderman, R.J., Lorenz, K., Manley, J., Pearlman, B.A., Wells, A., Zaks, A., and Zhang, T.Y. (2007) *Green Chem.*, **9**, 411.
- 96 Eissen, M. and Metzger, J.O. (2002) *Chem. Eur. J.*, **8**, 3580.
- 97 Andraos, J. (2005) *Org. Process Res. Dev.*, **9**, 149.
- 98 Jimenez-Gonzalez, C., Ponder, C.S., Broxterman, Q.B., and Manley, J.B. (2011) *Org. Process Res. Dev.*, **15**, 912.
- 99 Sanf elix, J., Mathieux, F., de la R ua, C., Wolf, M.-A., and Chomkhamri, K. (2013) *Int. J. Life Cycle Assessment*, **18**, 273.
- 100 <http://www.pre-sustainability.com/content/eco-indicator-99/> (accessed December 13, 2012).
- 101 de Vries, J.G., de Lange, B., de Vries, A.H.M., Mink, D., van Assema, F.B.J., Maas, P.J.D., and Hyett, D.J. (2006) EP1676838.
- 102 van Assema, F.B.J. and Sereinig, N. (2008) WO 2008031578.

