Direct Access to Highly Enantioenriched α-Branched Acrylonitriles through a One-Pot Sequential Asymmetric Michael Addition/Retro-Dieckmann/Retro-Michael Fragmentation Cascade

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Direct Access to Highly Enantioenriched α-Branched Acrylonitriles through a Formal Cross Rauhut-Currier Reaction

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A highly enantioselective synthesis of α-branched acrylonitriles is reported featuring an unprecedented formal cross Rauhut-Currier reaction consisting of an asymmetric Michael addition/retro-Dieckmann/retro-Michael fragmentation cascade. The method, which involves the use of an acrylonitrile surrogate, is practical, scalable and highly versatile, and provides a straightforward access to a wide range of enantioenriched nitrile-containing building blocks without using acrylonitrile or any source of cyanide. Most importantly, it offers a new tool to incorporate an acrylonitrile moiety in an asymmetric fashion.

Acrylonitrile-containing compounds are particularly attractive for the pharmaceutical and agrochemical industry.[1] Indeed, these bis-electrophiles are true launching pads towards numerous valuable synthons, with the cyano group being a precursor of amines, alcohols, aldehydes and carboxylic acids,[2] while the polarized alkene offers a plethora of possibilities, such as 1,4-additions,[3] cross-metatheses,[4] as well as controlled radical polymerizations[5] just to name a few. The acrylonitrile moiety can also be found in a number of biologically active natural products and other metabolites such as cyano-puupehenone[6] and borrelidin.[7]

Several methods allowing a direct access to this class of compounds have been reported over the years. The direct C–H functionalization of alkenes developed independently by Engle and Cravatt,[8] and by Studer[9] has emerged as a promising strategy. Alternatively, the hydrocyanation of an alkyne precursor reported by Ritter[10] and later by Nakao and Hiyama,[11] along with the α,β-dehydrogenation of activated alkyl nitriles,[12] represent valuable approaches. Regrettably however, none of these strategies have been applied to the synthesis of enantioenriched α-substituted acrylonitriles. This was eventually achieved using an enantioselective Morita-Baylis-Hillman reaction (Figure 1, **A**), however this strategy is limited to the use of sulfonyl imines and requires hazardous acrylonitrile[13] in excess.[14,15] As such, the development of a general method for the asymmetric synthesis of α-branched chiral acrylonitriles remains an important unaddressed synthetic challenge. To this end, we envisioned a catalytic enantioselective alternative to the Rauhut-Currier reaction (Figure 1, **B**)[16-18] using 4-cyano-3-oxotetrahydro thiophene (c-THT) as an acrylonitrile surrogate in a one-pot two-step sequence featuring an asymmetric Michael addition and a retro-Dieckmann/retro-Michael fragmentation (Figure 1, **C**). Although the use of c-THT as an acrylonitrile surrogate has already been reported in the past,[19,20] this is the first time it has been used in the context of asymmetric

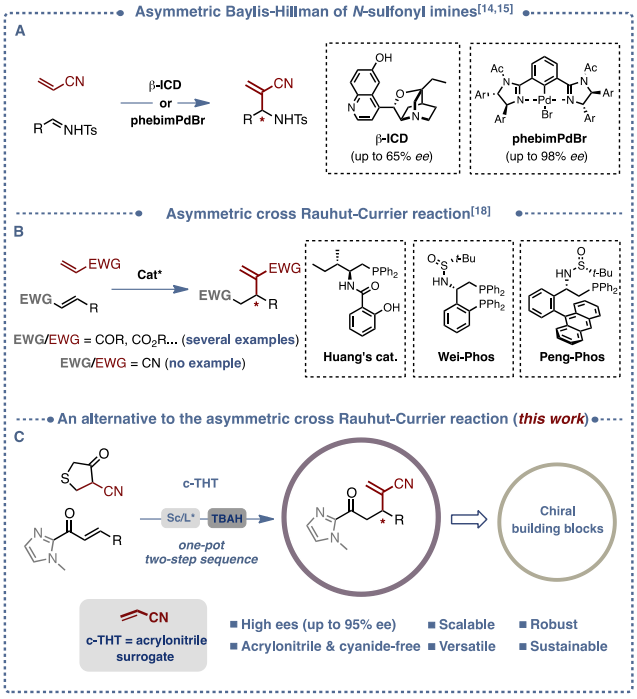


Figure 1. Development of a catalytic one-pot enantioselective Michael addition/retro-Dieckmann/retro-Michael fragmentation cascade for the synthesis of α-substituted acrylonitriles. (**A**) Asymmetric Baylis-Hillman of *N*-sulfonyl imines. (**B**) Enantioselective cross Rauhut-Currier reaction. (**C**) Generalized depiction of the proposed method.

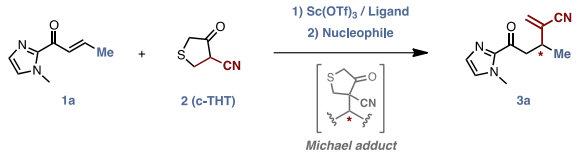
catalysis. Moreover, not only does this strategy allow to introduce the acrylonitrile moiety in an asymmetric and unbiased fashion without requiring the use of acrylonitrile[13] or any cyanide source, it also provides the first example of an enantioselective Rauhut-Currier type reaction applied to an acrylonitrile-containing substrate.[21]

We initiated our study using α,β-unsaturated 2-acylimidazole **1a** as a model substrate.[22] We also chose to work with scandium triflate for its robustness, practicality and unique Lewis acid properties.[23] Indeed, since its introduction by Desimoni and Evans in 2001,[24] scandium-based catalysts using PyBOX ligands have already met a frank success in various enantioselective conjugate addition processes.[25] To our delight, preliminary experiments using chiral PyBOX ligand **L1** (Table 1, entry 1) in $CHCl_3$ showed that the Michael addition proceeded smoothly at 0 °C in one hour, with an excellent 91% yield. Most importantly, this first attempt led to an encouraging 82% *ee* for the Michael adduct and prompted us to pursue the optimization.

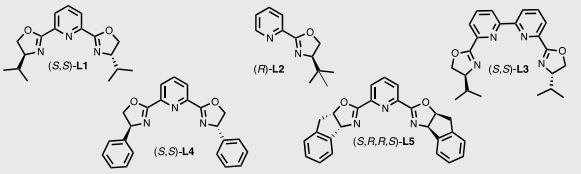
As we immediately opted to conduct the cascade in a one-pot fashion, we kept these initial conditions and turned our attention to the retro-Dieckmann fragmentation. In the original work by Baraldi and co-workers,[19] treatment with NaOH in a Et_2O/THF mixture was used, however these conditions led to a disappointing 33% yield and a slight erosion of the enantioselectivity (see SI, Table S1, entry 2). As sodium methoxide led to a very similar result (see SI, Table S1, entry 3), we decided to go for a hydroxide donor which would be soluble in organic solvents and therefore naturally selected tetrabutylammonium hydroxide (TBAH). To our delight, the retro-Dieckmann fragmentation occurred quasi instantaneously upon addition of the base (1.2 equiv.), affording the desired alkenyl nitrile **3a** in 61% yield and no erosion of the selectivity (Table 1, entry 2). The rapidity of the fragmentation under these conditions prompted us to continue with TBAH from this point on.

We next evaluated the influence of the ligand and started by varying its denticity. As expected, PyrOX-**L2** (49% yield, 0% *ee*) and BipyBOX-**L3** (4% yield, 8% *ee*) performed poorly, affording **3a** in low yields and low selectivities (Table 1, entries 3-4). This result was however not surprising considering the preferred coordination of scandium for tridentate ligands. We therefore backtracked to the initial PyBOX core with **L4**, which led to an improved albeit still low 38% *ee* (Table 1, entry 5). Interestingly, the use of **L5** not only drastically improved the yield and the enantioselectivity (68% yield, 95% *ee*), it also considerably reduced the reaction time (Table 1, entry 6). The superiority of the inda-PyBox ligand has been reported in the past.[26] Indeed, X-ray analysis of the Sc(III)-**L4** and the Sc(III)-**L5**

Table 1: Systematic study.



Entry	Ligand	Solvent	Nucleophile	Time	Yield[a]	*ee*[b]
1	L1	$CHCl_3$	-	1 h	91%	82%[c]
2	L1	$CHCl_3$	TBAH (1.2 eq)	1 h + **30 sec**	61%	83%
3	L2	$CHCl_3$	TBAH (1.2 eq)	12 h	49%	0%
4	L3	$CHCl_3$	TBAH (1.2 eq)	12 h	4%	8%
5	L4	$CHCl_3$	TBAH (1.2 eq)	1 h	56%	38%
6	**L5**	**$CHCl_3$**	**TBAH (1.2 eq)**	**30 min**	**68%**	**95%**
7	L5	CH_2Cl_2	TBAH (1.2 eq)	30 min	62%	64%
8	L5	CH_3CN	TBAH (1.2 eq)	12 h	40%	37%
9	L5	Toluene	TBAH (1.2 eq)	12 h	49%	54%
10	L5	THF	TBAH (1.2 eq)	12 h	59%	91%
11[d]	L5	$CHCl_3$	TBAH (1.2 eq)	12 h	59%	94%



Conditions: 1a (0.2 mmol), c-THT (0.22 mmol), $Sc(OTf)_3$ (10 mol%), ligand (11 mol%), 0.1 M, 0 °C. [a] Determined by ^1H NMR on the crude reaction mixture using CH_2Br_2 as an internal standard. [b] Determined by chiral HPLC. [c] Determined on the Michael adduct. [d] Using 1 mol% catalyst loading. [TBAH = tetrabutylammonium hydroxide]

complex indicates that the available space in the equatorial plane of the Sc(III)-**L5** complex is twice as small as the related Sc(III)-**L4** complex, which naturally leads to a higher face-differentiation in the Michael addition. It is worth noting that we also investigated other catalytic systems, including copper- and indium-based catalysts, but they generally resulted in lower selectivities (see SI, Table S1 and scope obtained with the Cu-based system). Interestingly, the use of indium triflate in combination with **L5** led to an inversion of the selectivity, an outcome which was also observed by Singh and co-workers.[27]

The solvent optimization showed relatively mixed results (see SI, Table S1, entries 9-17) but confirmed the superiority of $CHCl_3$ over all the other solvents, notably THF, which proved to be a strong candidate but was ruled out due to slow conversions and lower overall yields (Table 1, entry 9).

Ultimately, this optimization study shed some light on several aspects of this Sc-catalyzed sequence. Indeed, although complete conversion of the starting material to the corresponding Michael adduct was always observed, the presence of the α,β-unsaturated 2-acylimidazole precursor at the end of the reaction showcased the sensitive nature of the THT fragmentation which competes with a retro-Michael

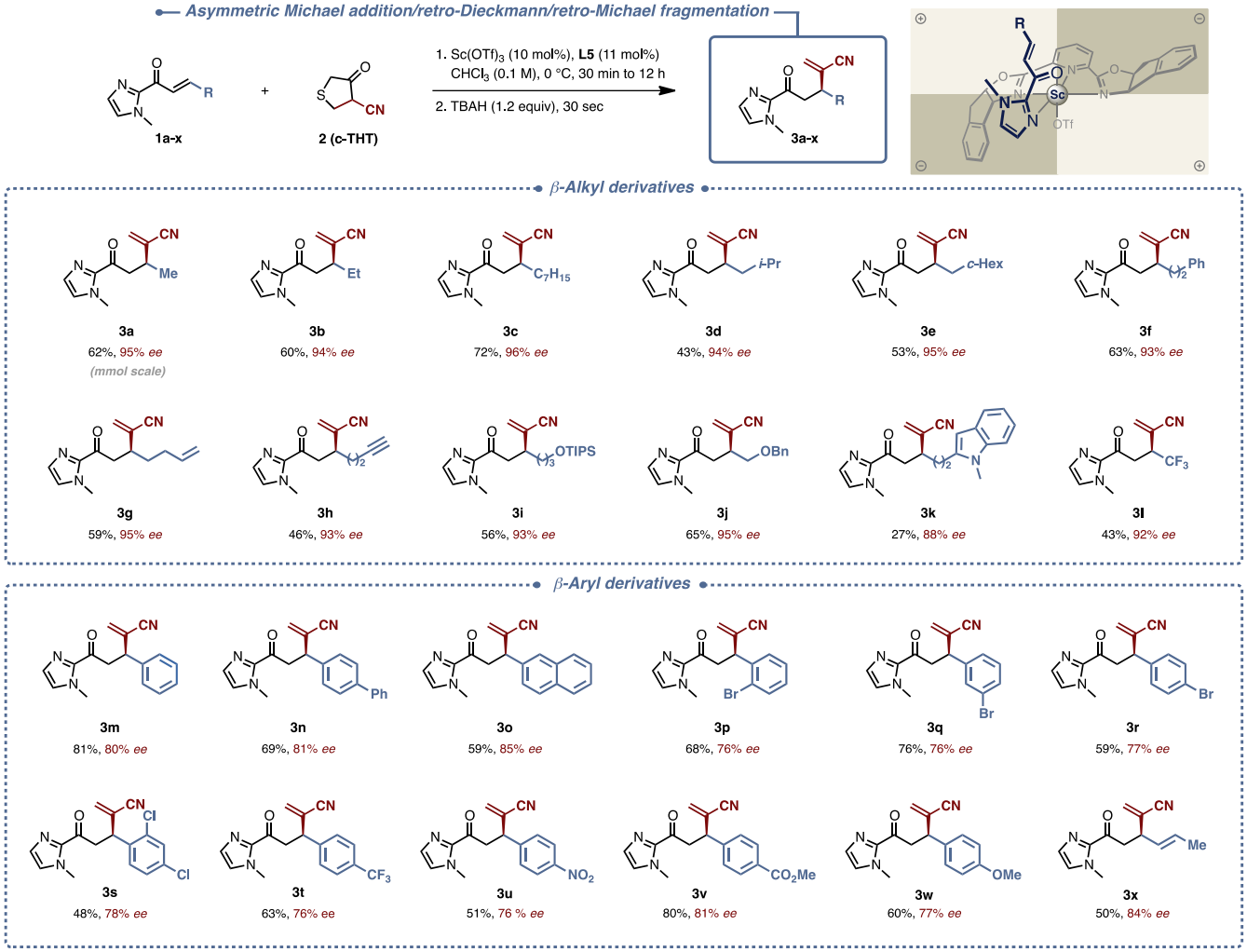
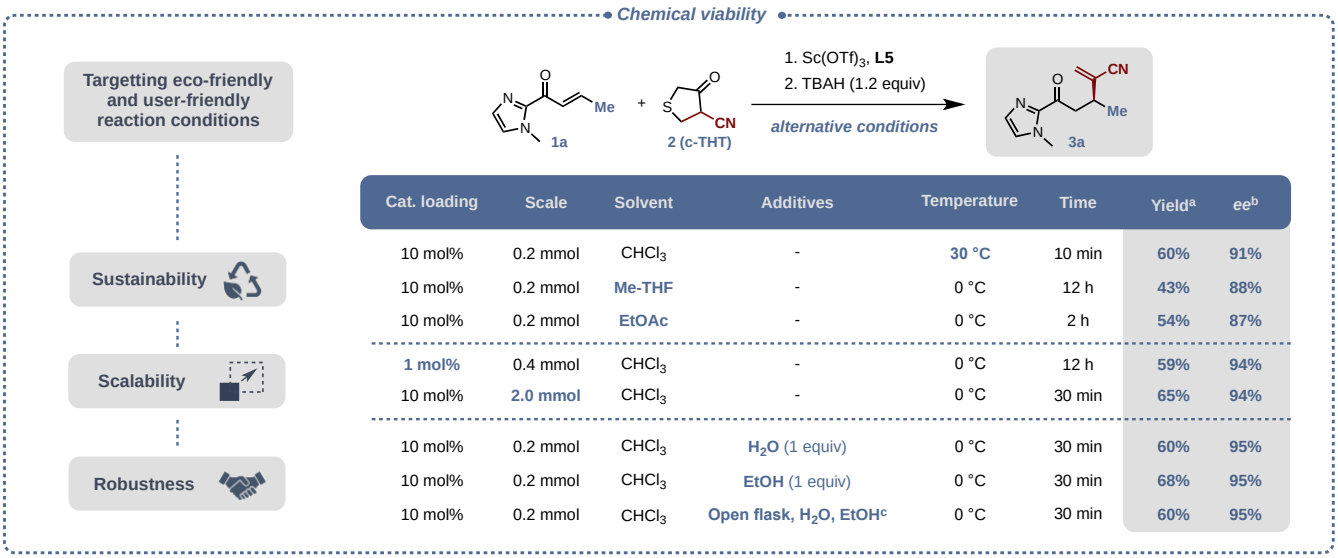


Figure 2. Reaction scope. Conditions: **1a-x** (0.27 mmol), c-THT **2** (0.3 mmol), $Sc(OTf)_3$ (10 mol%), (*S*,*R*,*R*,*S*)-**L5** (11 mol%), TBAH (1 M in MeOH, 0.32 mmol) upon completion of the Michael addition, 0.1 M in $CHCl_3$, 0 °C.

addition process. This side reaction is believed to arise from the abstraction by TBAH of one of the protons adjacent to the carbonyl moiety, the acidity of which is raised by the complexation with the Lewis acid, followed by an $E1_{CB}$-type elimination of the THT (See SI, Figure S1). Though this inherent side-reaction decreases the overall yield, the high reactivity of our catalytic system combined with its high selectivity as well as the simplicity of the method encouraged us to further explore the scope of this transformation. It is worth mentioning that all our attempts to conduct this reaction using acrylonitrile instead of c-THT were unproductive (see SI, Table S1, entries 27-29), stressing the potency of this approach to connect two "virtually" incompatible reactions: the asymmetric Michael addition and the α-alkylation of acrylonitriles.

We initiated the scope assessment with the exploration of various substrates bearing an aliphatic chain at the β-position of the enone (Figure 2). Interestingly, under our optimised conditions, the desired alkenyl nitriles **3b-f** were obtained in moderate to good yields and excellent enantioselectivities, with *ee*s ranging from 93 to 95%. Similarly, substrates bearing diversely functionalized side chains led to equally high selectivities. Notably, the presence of an alkene, an alkyne or an oxygen-containing moiety didn't decrease the selectivity (**3g-j**). Substrates decorated with an indole (88% *ee*, **3k**) or a trifluoromethyl (92% *ee*, **3l**) were also obtained with good to excellent *ees* albeit lower yields. The selectivity obtained with the substrate bearing a trifluoromethyl group is particularly encouraging as it proves that the reaction also tolerates strong electron-withdrawing groups.

Following these initial results, we also evaluated a series of β-aryl-substituted derivatives and rapidly realized that the presence of the aromatic group slightly decreased the selectivity as demonstrated by the results obtained with the phenyl (**3m**, 80% *ee*), the biphenyl (**3n**, 81% *ee*) and the naphthyl (**3o**, 85% *ee*) derivatives. A similar trend was also observed with substituted aromatic rings independently of the nature or the position of the substituent. Hence, a variety of



Cat. loading	Scale	Solvent	Additives	Temperature	Time	Yield[a]	ee[b]
10 mol%	0.2 mmol	$CHCl_3$	-	30 °C	10 min	60%	91%
10 mol%	0.2 mmol	Me-THF	-	0 °C	12 h	43%	88%
10 mol%	0.2 mmol	EtOAc	-	0 °C	2 h	54%	87%
1 mol%	0.4 mmol	$CHCl_3$	-	0 °C	12 h	59%	94%
10 mol%	2.0 mmol	$CHCl_3$	-	0 °C	30 min	65%	94%
10 mol%	0.2 mmol	$CHCl_3$	H_2O (1 equiv)	0 °C	30 min	60%	95%
10 mol%	0.2 mmol	$CHCl_3$	EtOH (1 equiv)	0 °C	30 min	68%	95%
10 mol%	0.2 mmol	$CHCl_3$	Open flask, H_2O, EtOH[c]	0 °C	30 min	60%	95%

Figure 3. Chemical viability of the method.[a] Determined by 1H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [b] Determined by chiral HPLC analysis. [c] Reaction ran in open air with H_2O (1 equiv) and EtOH (1 equiv).

functional groups including the more electron-withdrawing halides (**3p-s,** 76-78% *ee*), trifluoromethyl (**3t**, 76% *ee*), nitro (**3u**, 76% *ee*), and ester (**3v**, 81% *ee*) or the more electron-donating ether (**3w**, 77% *ee*) were shown to be compatible. The reaction conditions were also applied to a diene derivative in order to assess if any racemisation or rearrangement occurred upon TBAH addition. After slightly adjusting the reaction conditions (1 equiv. of TBAH), the corresponding acrylonitrile derivative **3x** was obtained in 50% yield and 84% *ee* without any noticeable racemization between the two steps.

To assess the chemical viability of the method, we decided to test its maximum operating conditions (Figure 3). As far as sustainability is concerned, the reaction showed a good temperature tolerance and didn't require cryogenic conditions to reach high levels of enantioselectivity. Similarly, the reaction could be run in technical grade ethyl acetate or Me-THF, two solvents considered as green solvents,[28] with once again no erosion of the selectivity; the resulting acrylonitrile **3a** being obtained in 87 and 88% *ee* respectively. Keeping in mind the possible implementation of the method to large scale processes, we ran two reactions in parallel; one on a 0.4 mmol scale using a ten-fold decrease in catalyst loading and one on a 2 mmol scale using the same catalyst loading as previously. Both reactions proceeded smoothly affording the desired product in roughly 60% yield and 94% *ee*. Finally we tested the robustness of the process by conducting the reaction in the presence of H_2O and/or EtOH under open-air and observed no noticeable decrease in either the yield or the enantioselectivity.

Finally, to demonstrate the synthetic utility of the resulting enantioenriched α-substituted acrylonitriles, several diversifications were performed (Figure 4). First, the acylimidazoyl moiety in **3a** was converted to the corresponding ester (**4**) and amide (**5**) using standard conditions [MeOTf, CH_2Cl_2, 0 °C, then MeOH or morpholine, DBU, rt].[26] Both products were obtained in good yields and with no erosion of the *ee*. We also showed that compounds such as **3a** could be readily α-alkylated under mild phase-transfer catalysis conditions [BnBr or allylBr, TBAB, CsOH, CH_2Cl_2, 0 °C].[29] The corresponding α-benzylated and α-allylated products **6** and **7** were obtained in good yields and a satisfying 7:2 diastereomeric ratio. The latter was eventually cyclised under ring-closing metathesis conditions [Grubb's II catalyst (5 mol%), CH_2Cl_2, 40 °C] to afford the corresponding cyclopentene **8** in 50% overall yield. The same ring-closing metathesis conditions applied to alkenyl nitrile **3g** led to yet another five-membered ring derivative (**9**) in 55% yield and a preserved 95% *ee*. Finally, compound **3m** was converted to the corresponding β-amino acid precursor **10**[30] in three steps and 41% overall yield without, once again, any noticeable erosion of the selectivity. Most importantly, some of these enantioenriched α-substituted acrylonitriles, particularly **4**[31] and **9**,[32,33] can potentially be used as key intermediates in the synthesis of a number of natural products such as the two naturally occurring monoterpenes mitsugashiwa-lactone and dolichodial, the monoterpenol, lasiol, the true trail pheromone of Pharaoh's ant, faranal, and the neurotoxin, kalkitoxin, just to name a few.

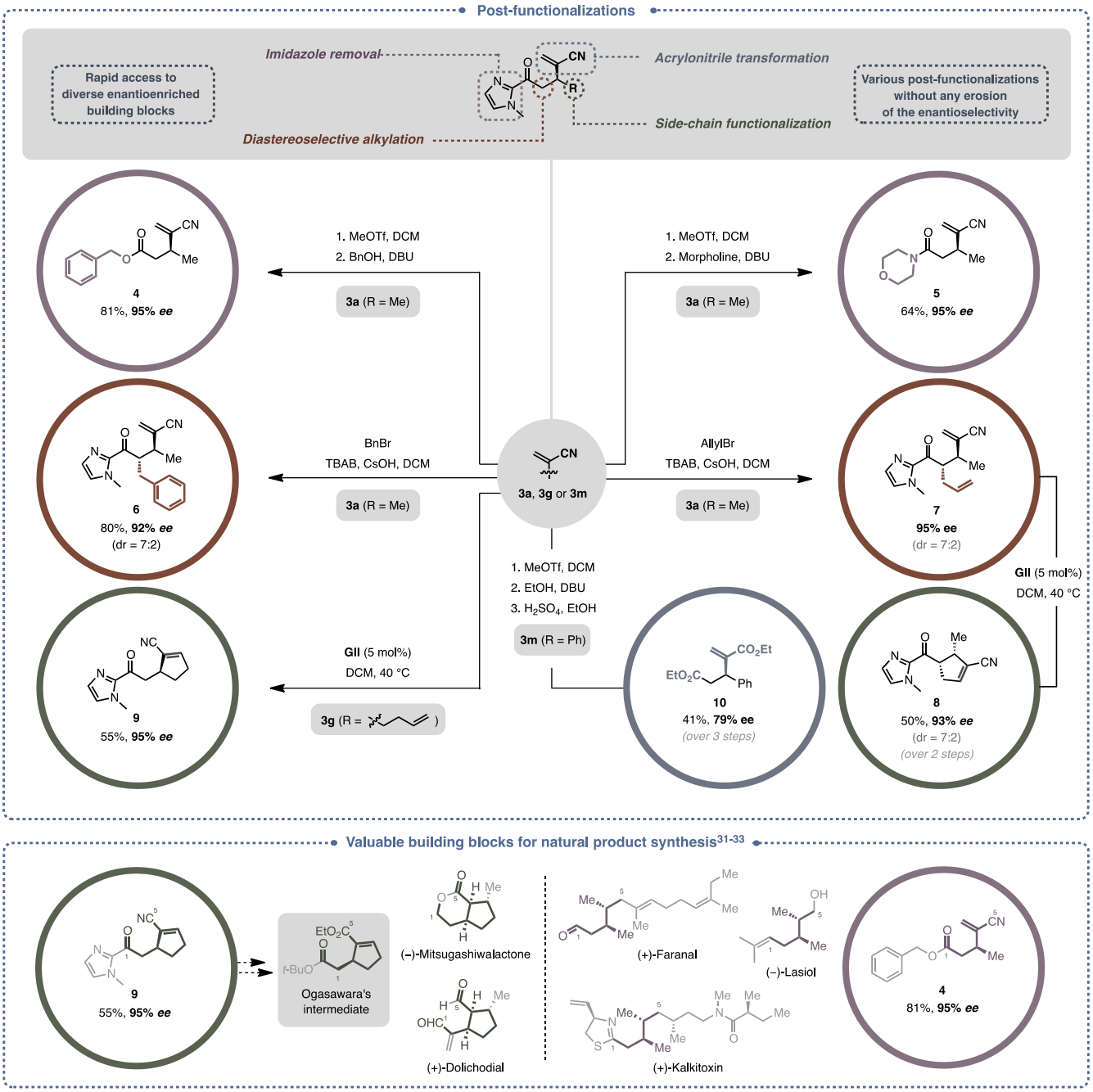


Figure 4. Post-functionalizations.

In summary, we have developed a catalytic, one-pot two-step sequence featuring an asymmetric Michael addition and a retro-Dieckmann/retro-Michael fragmentation, using 4-cyano-3-oxotetrahydro-thiophene (c-THT) as an acrylonitrile surrogate, which affords cross Rauhut-Currier type products in high *ees*. More importantly, this asymmetric cascade is acrylonitrile-free, cyanide-free, easy to set up, scalable and robust, and offers a direct access to highly enantioenriched α-substituted acrylonitriles, which ultimately proved to be tolerant and flexible towards carefully chosen post-functionalizations, consequently providing diversified and valuable enantioenriched building blocks. The concept, through the latent acrylonitrile surrogate (c-THT) and the retro-Dieckmann/retro-Michael fragmentation, virtually connects the asymmetric Michael addition and the α-alkylation of acrylonitrile, two reactivities which, at first glance, appear to be irreconcilable. With this in mind and considering the importance of the acrylonitrile motif in medicinal, agrochemical and polymer chemistry, we believe this method will become an essential tool in the synthetic chemist's toolbox.

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Notes

The authors declare no competing financial interest.