RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2014, **4**, 40199

Indium-assisted aluminium-based stereoselective allylation of prostereogenic α,α-disubstituted cycloalkanones and imines†

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Received 8th May 2014
Accepted 6th August 2014

DOI: 10.1039/c4ra04293j

www.rsc.org/advances

The use of a catalytic amount of $InCl_3$ in combination with Al^0 for the allylation of a variety of prostereogenic α,α-disubstituted (hindered) cycloalkanones, 1,2-dione-based systems and various imino systems (C=N functional groups) is reported. The stereoselective $InCl_3$-catalyzed Al-based allylation of various 2-substituted-2-carbethoxycycloalkanones gave the corresponding products with moderate to excellent diastereoselectivity. The allylation and propargylation of imines including α-imino esters using a catalytic amount of $InCl_3$ in combination with Al^0 gave the corresponding allylated and propargylated compounds in moderate to good yields. If γ-substituted allylic halides were added to imino compounds, low to very good diastereoselectivity was obtained. The allylation of chiral *N*-*tert*-butylsulfinyl imine systems gave the corresponding products in moderate yields with good to excellent diastereoselectivity.

Introduction

The addition of organometallic reagents to carbonyl (C=O) and imino (C=N) functional groups is one of the most important types of organometallic reactions. The addition of the allylmetals to carbonyl (C=O) and imino (C=N) functional groups is considered to be an imperative C–C bond forming protocol. This method is widely used for assembling functionalized acyclic- or cyclic-homoallylic alcohols/amines which have one or more stereocenters with a high degree of stereo- and regiocontrol.[1] Notably, the allylation step is considered to show immense scope in multi-step synthesis, after the allylation reaction, the olefin moiety present in the product can be subjected to a wide range of functional group transformations.

A variety of allylmetal reagents prepared using metals such as B, Ce, Cu, Li, Mg, Mn, Pb, Sn, Ti and Zn, and so on, have been very well utilized and thoroughly documented for performing, typically, the Grignard-type allylation of the carbonyl (C=O) and imino (C=N) functional groups.[1,2] However, in recent years, the Barbier-type addition reaction[3–5] of allylmetals involving some of the previously mentioned metals together with other metals[6–11] such as Bi, Ga and In, and so on, to carbonyl (C=O) and imino (C=N) functional groups has been widely recognized. This protocol has a benefit as the prior preparation of allylmetal reagents is not necessary and the allylation reaction can be achieved by directly reacting the carbonyl compound or imine, metal powder and allylic halide. Notably, since the report by Araki in 1988,[6a] the indium-based Barbier-type addition of allylic reagents to carbonyl (C=O) and imino (C=N) systems frequently offered very high stereoselectivity and has been applied for the synthesis of a variety of functionalized molecules containing one or more stereocenters.[1,2,6] Generally, the stoichiometric amount of allylmetal reagents or metals (*e.g.*, Bi, Ga, and In, and so on) are required for performing the Grignard or Barbier-type of allylation reactions.[1–11]

Apart from using indium in organic synthesis, there has been an increased use of indium-based materials in information technology industries which are involved in developing liquid crystal display (LCD) and television (TV) screens, solar energy technology, semiconductors, and so on. Because of this reason the cost of indium metal has increased.

In view of the previously mentioned points, there is a need for finding alternative metals, especially, for replacement of Ga and In, and if the In-based organic transformations can be performed using a catalytic amount of In, then the practicality and adaptability of In metal in organic synthesis could be increased.[12] The use of a catalytic amount of indium in combination with other metals such as Al or Zn, and so on, could be an alternative strategy[12,13] and notably, Al metal[14] is relatively inexpensive and is considered to be less toxic when compared to other metals such as Ga or In. In recent years, there have been some remarkable reports demonstrating the allylation of carbonyl compounds using a catalytic amount of In^0 or In(III) salts in combination with Al or Zn or other metals.[12] Research by Butsugan, Hirashita, Preite, Knochel, Augé, and

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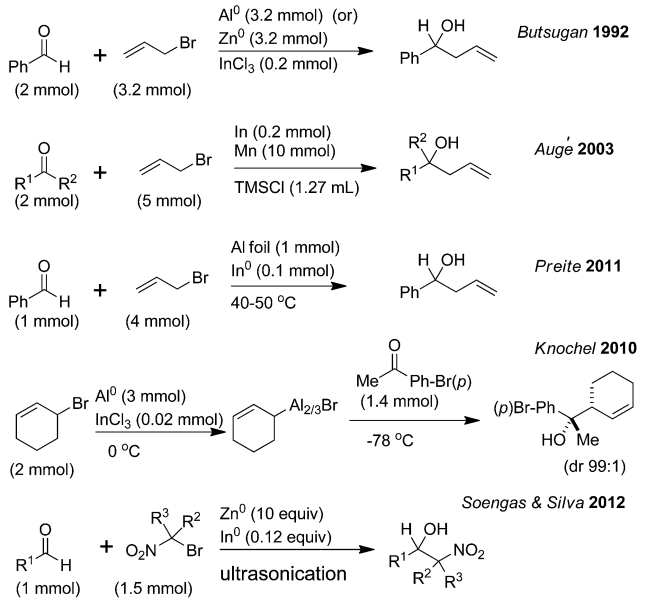
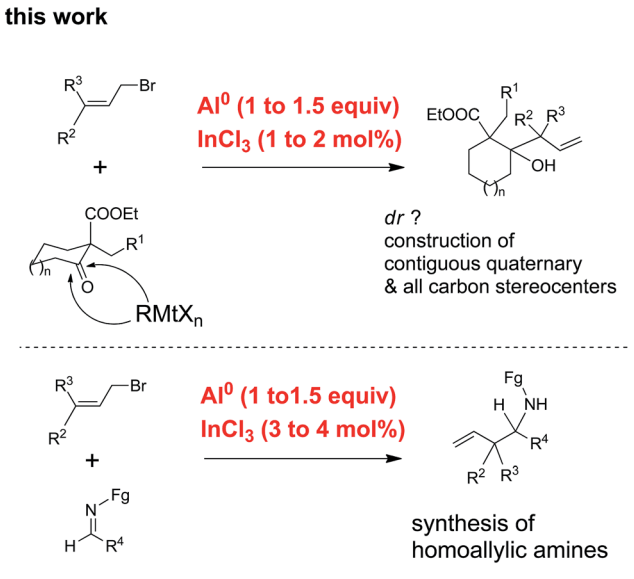
† Electronic supplementary information (ESI) available: Copies of NMR spectra. CCDC 1001586 and 1001554. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra04293j



Scheme 1 Examples from literature demonstrating different methods for the allylation of carbonyl compounds using a catalytic amount of In^0 or In(III) salts in combination with Al or Zn or other metals.



Scheme 2 Diagrammatic representation of the $InCl_3$/Al system for the stereoselective allylation of prostereogenic α,α-disubstituted cycloalkanones and imino compounds (C=N systems).

Takai has demonstrated the allylation of carbonyl compounds using a catalytic amount of In^0 or In(III) salts in combination with Al and other metals (Scheme 1).[13]

Although Al metal belongs to the same group as In and Ga, except in the research by Knochel *et al.* on the use of $InCl_3$ in combination with Al, the direct use of Al^0 powder for the stereoselective allylation of carbonyl compounds to give more than one stereocenter has not been extensively explored using a Barbier-type reaction.[12–14] Furthermore, to the best of our knowledge, the allylation of imino (C=N bond systems) functional groups has not been reported using In in combination with Al metal powder. Continuing our interest in exploring the In-based stereoselective allylation of carbonyl (C=O) and imino (C=N) functional groups, we report in this paper on our efforts to use $InCl_3$/Al as an economically alternative bimetallic system for the stereoselective allylation of prostereogenic α,α-disubstituted cycloalkanones[15,16] and various imino compounds (C=N bond systems).[17,18a,b]

Results and discussion

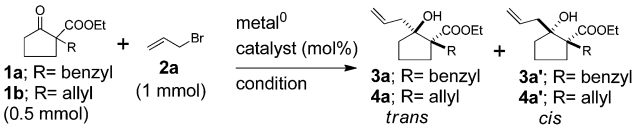
Initially, it was envisaged that the use of a catalytic amount of $InCl_3$ in combination with Al for the diastereofacial selective allylation of prostereogenic α,α-disubstituted (hindered) cycloalkanones and the stereoselective construction of a stereoarray having consecutively attached, tertiary carbinol- and an all carbon-based stereocenter in functionalized carbocyclic compounds, would be investigated.[15,16] We performed the optimization reactions using the substrate 2-benzyl-2-carbethoxycyclopentanone (**1a**) or 2-allyl-2-carbethoxycyclopentanone (**1b**), allyl bromide, Al metal powder and a catalyst under Barbier-type reaction conditions (Table 1). The Barbier-type allylation of the substrate **1a** or **1b** using Al^0 powder in the absence of any catalyst gave the products **3a** and **4a**, with yields 65 and 20%, respectively (entries 1 and 2, Table 1). However, the Barbier-type allylation of substrate **1a** with $InCl_3$ (40 mol%) in the absence of Al^0 powder did not give any product (entry 3, Table 1). The Barbier-type allylation of the substrates **1a** or **1b** using Al^0 powder (0.5–1 mmol) in the presence of a catalytic amount of $InCl_3$ or $InBr_3$ (5 or 10 mol%) in anhydrous tetrahydrofuran (THF) successfully gave the product **3a** or **4a** (*dr* 98 : 2, *trans* isomer) with a yield of 95% (entries 4–6, Table 1).

Subsequently, the Barbier-type allylation of **1b** using Al^0 powder (0.55 mmol) in the presence of just 2 mol% of $InCl_3$ in anhydrous THF gave the product **4a** (*dr* 98 : 2, *trans* isomer) with a yield of 95% (entry 7, Table 1). Furthermore, the allylation of **1b** in other solvents such as DCM or DMF or MeCN gave the product **4a** (*dr* 98 : 2, *trans* isomer) with yields of 91%, <5%, 90%, respectively (entries 8–10, Table 1). The allylation of **1b** using Al^0 powder in the presence of catalytic amount of $InCl_3$ in THF–water mixture did not give any product (entry 11, Table 1).

Then, we tried to use different catalysts instead of $InCl_3$ for the Barbier-type allylation of **1b**. We found that the allylation of **1b** using Al^0 powder in the presence of a catalytic amount of $SnCl_2$ or $ZnCl_2$ or $GaClO_4$ was ineffective (entries 12–14, Table 1). However, the allylation of **1b** progressed smoothly when we used Al^0 powder in the presence of a catalytic amount of $In(OTf)_3$ or $In(OAc)_3$ and gave the product **4a** (*dr* 98 : 2, *trans* isomer) with a yield of 95% (entries 15 and 16, Table 1). When we used $BiCl_3$ (8 mol%) as a catalyst, the product **4a** was obtained with a yield of 30% (entry 17, Table 1).

Subsequently, we carried out the Barbier-type allylation of **1a** using Al^0 powder (1 mmol) in the presence of catalytic amounts

Table 1 $InCl_3$/Al-based Barbier-type allylation of substrates **1a**/**1b** and optimization of reaction conditions[a]



Entry	R	$Metal^0$ (mmol)	Catalyst (mol%)	Solvent (mL)	Temp (°C)	*t* (h)	Yield (%) (*dr*)
1	Benzyl	Al (0.5)	Nil	THF (1.5)	rt	10	65 (98 : 2)
2	Allyl	Al (1)	Nil	THF (1.5)	rt	12	20 (N.D.)
3	Benzyl	Nil	$InCl_3$ (40)	THF (1.5)	rt	10	0 (—)
4	Benzyl	Al (0.5)	$InCl_3$ (10)	THF (1.5)	rt	12	95 (98 : 2)
5	Allyl	Al (0.5)	$InCl_3$ (5)	THF (1.5)	rt	15	95 (98 : 2)
6	Benzyl	Al (1)	$InBr_3$ (10)	THF (1.5)	rt	4	95 (98 : 2)
7	Allyl	Al (0.55)	$InCl_3$ (2)	THF (1.5)	rt	1	95 (98 : 2)
8	Allyl	Al (0.5)	$InCl_3$ (2)	DCM (1.5)	rt	2	91 (98 : 2)
9	Allyl	Al (0.5)	$InCl_3$ (3.5)	DMF (1.5)	rt	1.5	<5 (—)
10	Allyl	Al (0.5)	$InCl_3$ (2)	MeCN (1.5)	rt	7	90 (98 : 2)
11	Allyl	Al (0.75)	$InCl_3$ (5)	THF (3)/H_2O (1)	rt	9	0 (—)
12	Allyl	Al (1)	$SnCl_2$ (5)	THF (1.5)	rt	12	0 (—)
13	Allyl	Al (0.75)	$ZnCl_2$ (20)	THF (1.5)	rt	7	0 (—)
14	Allyl	Al (0.55)	$Ga(ClO_4)$ (5)	THF (1.5)	rt	2	0 (—)
15	Allyl	Al (0.55)	$In(OTf)_3$ (1)	THF (1.5)	rt	1	95 (98 : 2)
16	Allyl	Al (0.55)	$In(OAc)_3$ (1)	THF (1.5)	rt	2	95 (98 : 2)
17	Allyl	Al (0.55)	$BiCl_3$ (8)	THF (1.5)	rt	26	30 (N.D.)
18	Benzyl	Al (1)	In (10)	THF (1.5)	rt	9	95 (98 : 2)
19	Allyl	Al (0.5)	Bi (20)	THF (1.5)	rt	7	85 (98 : 2)
20	Allyl	Al (1)	Zn (10)	THF (1.5)	rt	8	40 (N.D.)
21	Benzyl	Al (1)	Sn (10)	THF (1.5)	rt	12	0 (—)

[a] All the reactions were carried out under Barbier-type reaction conditions. The substrate **1a** or **1b** was treated with allyl bromide, Al^0 and a catalytic amount of $InCl_3$ or In^0 or other catalyst in one pot. N.D. = not determined; DCM = dichloromethane; DMF = dimethylformamide; $In(OTf)_3$ = indium(III) trifluoromethanesulfonate, $In(OAc)_3$ = indium triacetate.

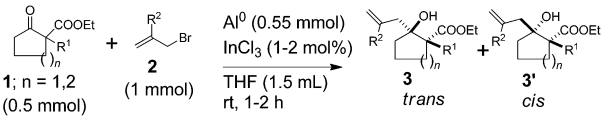
of In^0 powder (10 mol%) in anhydrous THF which gave the product **3a** (95%, *dr* 98 : 2, *trans* isomer) (entry 18, Table 1). Similarly, the allylation of the substrate **1b** using Al^0 powder (0.5–1 mmol) in the presence of catalytic amounts of other metals such as Bi^0 or Zn^0 (10–20 mol%) gave the product **4a** with yields of 85% and 40%, respectively (entries 19 and 20, Table 1). The allylation of **1a** using a catalytic amount of Sn^0 powder together with Al^0 powder did not give the product **3a** (entry 21, Table 1).

Next, the scope and applicability of this allylation protocol using a catalytic amount of $InCl_3$ in combination with Al^0 powder was tested with a variety of prostereogenic α,α-disubstituted (hindered) cycloalkanones and the construction of functionalized carbocycles having consecutively attached tertiary carbinol- and an all carbon-based stereocenter is shown in Table 2. Under the optimized reaction conditions, we carried out the Barbier-type allylation of various prostereogenic 2-benzyl-2-carbethoxycyclopentanones **1a–h** and 2-alkyl-2-carbethoxycyclopentanones **1i**, **1j** with **2a** or **2b** using a catalytic amount of $InCl_3$ (1–2 mol%) in combination with Al^0 powder (0.55 mmol) in anhydrous THF. These reactions progressed smoothly and gave the corresponding products **3a–i** (*trans* isomers) with yields of 66–95% (entries 1–9, Table 2) with very high diastereoselectivity (*dr* 98 : 2). The Barbier-type allylation of 2-alkyl/aryl-2-carbethoxycyclohexanones **1k–n** using a catalytic amount of $InCl_3$ (1–2 mol%) and Al^0 powder (0.55 mmol) gave the products **3j–m** which had a relatively low diastereoselectivity (entries 10–13, Table 2).

Next, the allylation of the substrate **1b** with 2,3-dibromoprop-1-ene (**2c**) failed to give the expected product **3n** (entry 14). The allylation of 2-allyl-2-carbethoxycyclopentanone (**1b**) and ethyl 2-acetyl-2-benzylpent-4-enoate (**1o**) gave the allylated products **4a** (96%, *dr* 98 : 2) and **3o** (81%, *dr* 55 : 45), respectively (entries 15 and 16, Table 2). Consequently, the allylation of ethyl 3-allyl-1-benzyl-4-oxopiperidine-3-carboxylate (**1p**) gave the piperidine derivative **3p** with a yield of 55% (*dr* 60 : 40, entry 17, Table 2).

The allylation of a relatively hindered cyclopentanone system ethyl 1-benzhydryl-2-oxocyclopentanecarboxylate (**1q**) was performed and the product **3q** was obtained with a yield of 87% (*dr* 95 : 5, entry 18). For the substrates **1k–p**, the corresponding products **3j–m** and **3o**, **3p** were obtained with a lower diastereoselectivity than the products **3a–i**, **4a**, and **3q**; this may be because of the involvement of a less rigid transition state[16c] under the experimental conditions. The Barbier-type allylation of the substrates **1a** and **1c** using allyl chloride, Al metal powder and a catalytic amount of $InCl_3$ (3 mol%) in THF at 35 °C and 45 °C progressed smoothly and gave the products **3a** and **3b** with a yield of 90% (entries 19 and 20, Table 2).

Table 2 Indium-catalyzed Al-based allylation of α,α-disubstituted cycloalkanones and the construction of functionalized carbocycles[a]



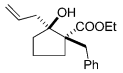
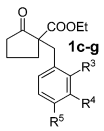
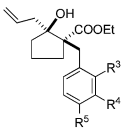
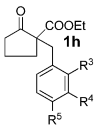
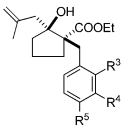
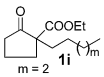
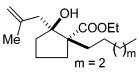
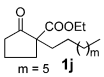
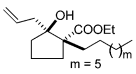
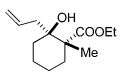
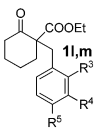
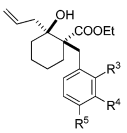
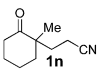
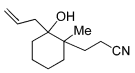
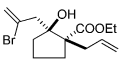
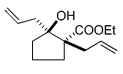
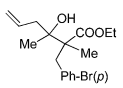
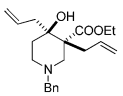
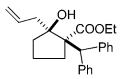
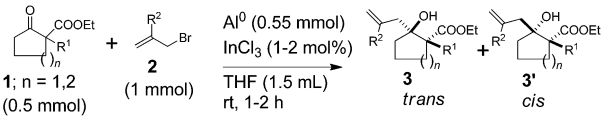
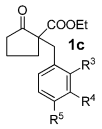
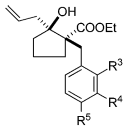
Entry	Ketone	Allyl bromide	Product	Yield (%) (*dr*)
1				**3a**; 95 (98 : 2)
2				**3b**; R^3, R^4 = H, R^5 = Br, 92 (98 : 2)
3				**3c**; R^4, R^5 = H, R^3 = F, 85 (98 : 2)
4				**3d**; R^3, R^4 = H, R^5 = Me, 87 (98 : 2)
5				**3e**; R^3, R^4 = H, R^5 = NO_2, 76 (98 : 2)
6				**3f**; R^4, R^5 = Cl, R^3 = H, 78 (98 : 2)
7				**3g**; R^3, R^5 = Cl, R^4 = H, 66 (98 : 2)
8				**3h**: 78 (98 : 2)
9				**3i**: 87 (98 : 2)
10				**3j**: 89 (60 : 40)
11				**3k**; R^3, R^4 = H, R^5 = Br, 91 (56 : 44)
12				**3l**; R^3, R^5 = H, R^4 = Cl, 89 (60 : 40)
13				**3m**: 60 (60 : 40)
14				**3n**: 0
15				**4a**: 96 (98 : 2)
16				**3o**: 81 (55 : 45)
17				**3p**: 55 (60 : 40)
18				**3q**: 87 (95 : 5)
19[b]				**3a**: 90 (98 : 2)

Table 2 (*Contd.*)

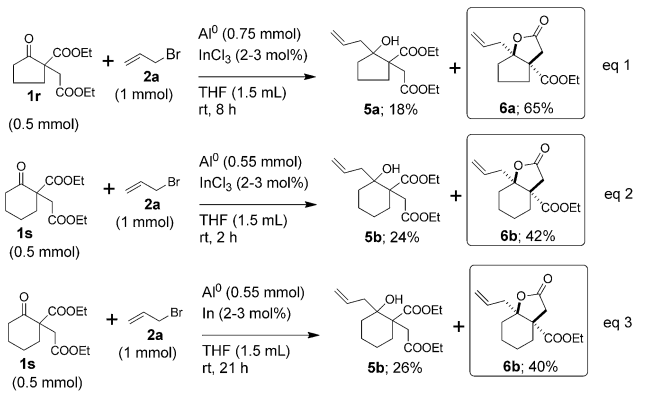


Entry	Ketone	Allyl bromide	Product	Yield (%) (*dr*)
20[c]				**3b**; R^3, R^4 = H, R^5 = Br, 90 (98 : 2)

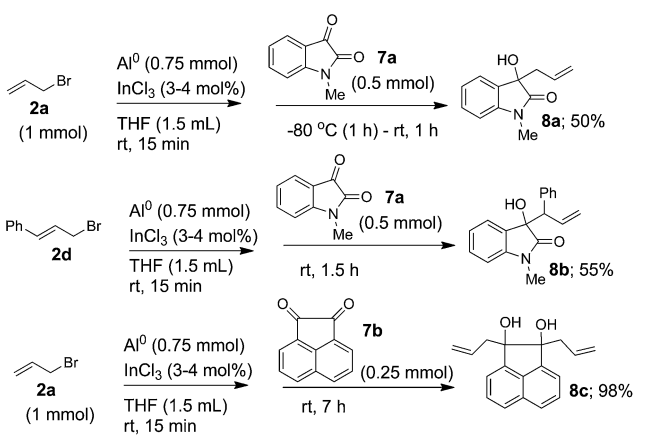
[a] All the reactions were carried out under Barbier-type reaction conditions. Substrate **1** was treated with allyl bromide, Al^0 and a catalytic amount of $InCl_3$ in one pot. [b] The reaction was performed using Al^0 (0.55 mmol) and $InCl_3$ (3 mol%) at 35 °C for 15 h. [c] The reaction was performed using Al^0 (0.55 mmol) and $InCl_3$ (3 mol%) at 45 °C for 7 h.

Next, we performed the allylation of prostereogenic ethyl 1-(2-ethoxy-2-oxoethyl)-2-oxocycloalkanecarboxylates, **1r** and **1s** with allyl bromide by using a catalytic amount of $InCl_3$ in combination with Al^0 powder in anhydrous THF. The allylation of **1r** and **1s** gave both the allylation products **5a**, **5b** as well as the bicyclic lactones **6a**, **6b**, respectively (eqn (1), (2) and Scheme 3).[18a] In these reactions, the bicyclic lactones **6a** (65%) and **6b** (42%) were obtained because the substrates **1r** and **1s** have an ester group at an appropriate distance and thereby underwent an *in situ* lactonization[18a] during the allylation reaction under the experimental conditions. In order to increase the yield of the bicyclic lactone **6b**, a catalytic amount of In^0 was used instead of $InCl_3$, however, there was no improvement in the yield of the lactone **6b** (eqn (3), Scheme 3).

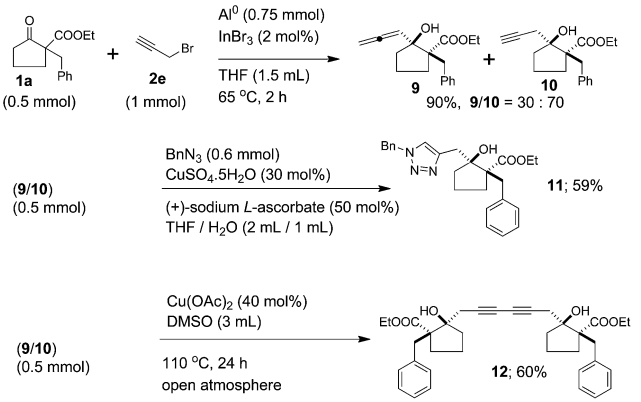
Subsequently, the allylation reactions of the dicarbonyl compound **7a** (*N*-methylisatin) with allyl bromide and cinnamyl bromide using a catalytic amount of $InCl_3$ in combination with Al^0 powder were performed. In these reactions the oxindole products **8a** and **8b** were obtained with yields of 50% and 55%, respectively (Scheme 4). The cinnamylation of **7a** gave the product **8b** which had good diastereoselectivity (*dr* 90 : 10, Scheme 4). The allylation of the dicarbonyl compound **7b** with allyl bromide using a catalytic amount of $InCl_3$ in combination with Al^0 gave the bis-allylated compound **8c** (98%, Scheme 4). Additionally, the scope of this protocol was tested for the propargylation of the substrate **1a** (Scheme 5). The propargylation of cyclic ketone **1a** gave the allene product **9** and the propargylated product **10** with a yield of 90% (combined yield of **9**/**10**). Our efforts to separate these two products were not successful and the products **9**/**10** were isolated as a mixture of compounds. Furthermore, we decided to perform the click reaction[19c] and Glaser–Eglinton–Hay sp–sp coupling[19d] with a mixture of compounds **9**/**10**. Accordingly, the corresponding products **11** (59% yield) and **12** (60% yield) were isolated in a pure form after the column chromatography purification (Scheme 5).



Scheme 3 Indium-catalyzed allylation of ethyl 1-(2-ethoxy-2-oxoethyl)-2-oxocycloalkanecarboxylates **1r**, **1s**. All the reactions were carried out under the Barbier-type reaction conditions. The substrate **1r** or **1s** was treated with allyl bromide, Al^0 powder and a catalytic amount of $InCl_3$ in one pot.



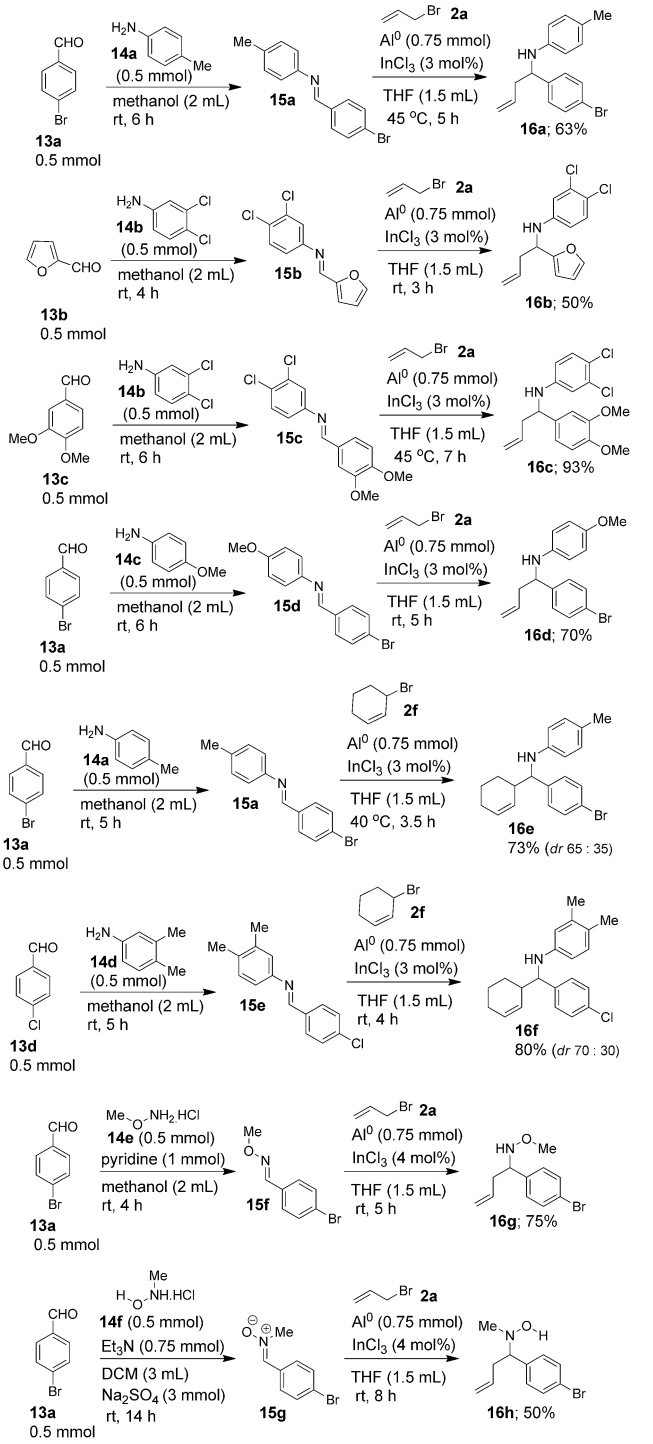
Scheme 4 $InCl_3$-catalyzed Al^0-based allylation of 1,2-diones. In all the reactions, the allylmetal was first prepared separately and then the dione **7a** or **7b** was added.



Scheme 5 $InCl_3/Al^0$-based propargylation of **1a** followed by click and Glaser–Eglinton–Hay reactions. The substrate **1a** was treated with propargyl bromide, Al^0 powder and a catalytic amount of $InCl_3$ in one pot.

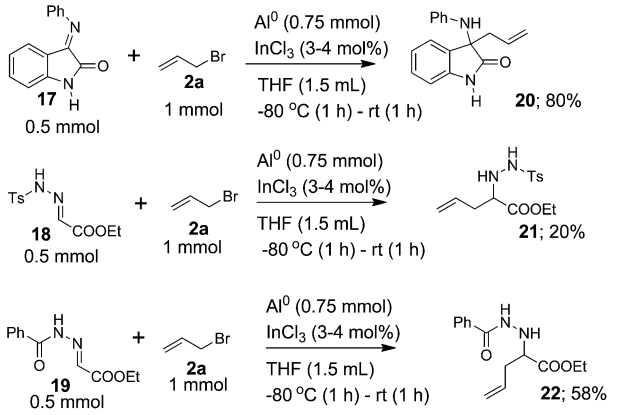
Next, we focused our attention on investigating the C–C bond forming protocol and the synthesis of homoallylic amines *via* the allylation of imino (C=N) functional groups using a catalytic amount of $InCl_3$ in combination with Al^0 metal powder. There have been some exceptional reports in the literature on the In-catalyzed allylation of carbonyl compounds,[12] however, to the best of our knowledge, the allylation of imino (C=N bond systems) functionality has not been explored using a catalytic amount of In in combination with a cheap metal such as Al.[6,17,18a,b] To start with, a series of C=N bond systems, such as the imine compounds **15a–e**, oxime **15f** and nitrone **15g** (Scheme 6), were prepared. The corresponding imino compounds **15a–g** were added to a THF solution of corresponding allylmetal reagents which were prepared separately from allyl bromide (**2a**) or 3-bromocyclohex-1-ene (**2f**), a catalytic amount of $InCl_3$ (3–4 mol%) and Al^0 metal powder (0.75 mmol). All these reactions successfully gave the homoallylic amines **16a–h** with a yield of 50–93%. For the allylation of substrates **15a** and **15e** with 3-bromocyclohex-1-ene (**2f**), the corresponding products **16e** and **16f** were obtained with a moderate diastereoselectivity under the experimental conditions used.

Next, we prepared the next series of C=N bond systems such as the isatin-derived imine [(*E*)-3-(phenylimino)indolin-2-one] (**17**) and the ethyl glyoxalate-derived imino systems (*E*)-ethyl 2-(2-tosylhydrazono)acetate (**18**) and (*E*)-ethyl 2-(2-benzoylhydrazono)acetate (**19**) (Scheme 7). Then, we added imino compounds **17–19** to a THF solution of allylmetal reagent prepared separately from allyl bromide (**2a**), $InCl_3$ (3–4 mol%) and Al^0 metal powder (0.75 mmol). The allylation of **17** gave the product 3-allyl-3-(phenylamino)indolin-2-one (**20**) with a yield of 80%. The product ethyl 2-(2-tosylhydrazinyl)pent-4-enoate (**21**) was obtained with a yield of only 20%. The allylation of *N*-acylhydrazono ester **19** gave the product ethyl 2-(2-benzoylhydrazinyl)pent-4-enoate (**22**) with a yield of 58% (Scheme 7). We also carried out the In-catalyzed Al-based prenylation of *N*-aryl α-imino ester **23a** and the propargylation of a series of *N*-aryl α-imino esters **23a–c** (Scheme 8). These reactions

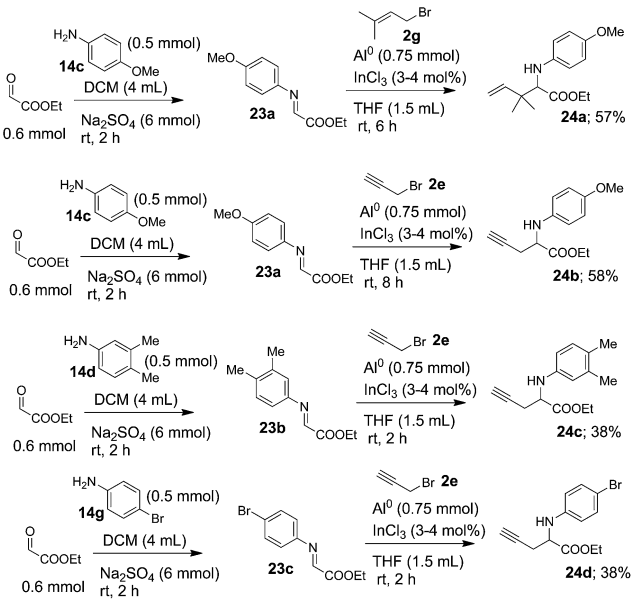


Scheme 6 $InCl_3$-catalyzed Al^0-based allylation of C=N bond systems **15a–g**. In all the reactions imino compounds **15a–g** and allylmetal were prepared separately and then the corresponding imino compounds **15a–g** were added to the round bottomed flask containing the allylmetal reagent obtained from **2a** or **2f**.

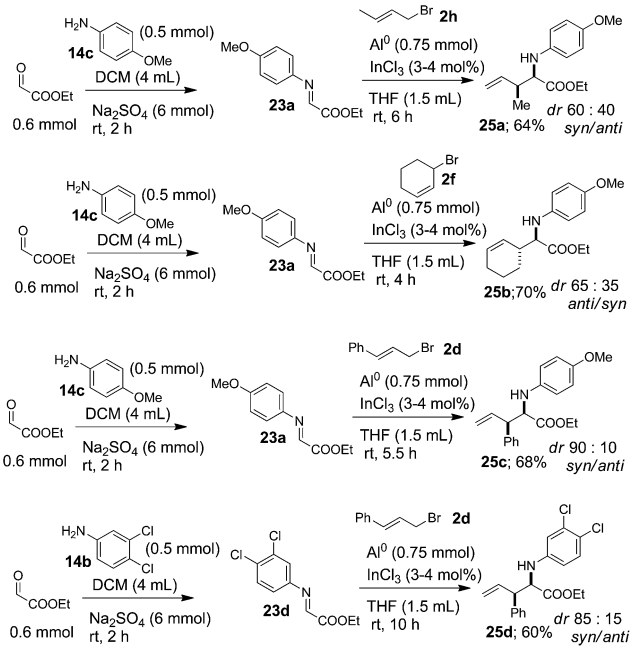
led to the synthesis of γ,δ-unsaturated β,β′-dimethyl *N*-aryl α-amino acid derivative **24a** (with a yield of 57%) and a variety of propargylated products, ethyl 2-((aryl)amino)pent-4-ynoates **24b–d** with yields of 38–58% (Scheme 8).



Scheme 7 $InCl_3$-catalyzed Al^0-based allylation of C=N bond systems **17–19**. In all the reactions the imino compounds **17–19** and the allylmetals were prepared separately and then the corresponding imino compounds **17–19** were added to the round bottomed flask containing the allylmetal reagent.



Scheme 8 $InCl_3$-catalyzed Al^0-based propargylation of C=N bond systems. The imino compounds **23a–c** were prepared separately. In the reactions involving the formation of products **24a**, **24b**, imine **23a** was treated with **2g** or **2e**, Al^0 and $InCl_3$ in one pot. In the reactions involving the formation of products **24c**, **24d**, imines **23b**, **23c** were added to propargyl metal reagents prepared separately.



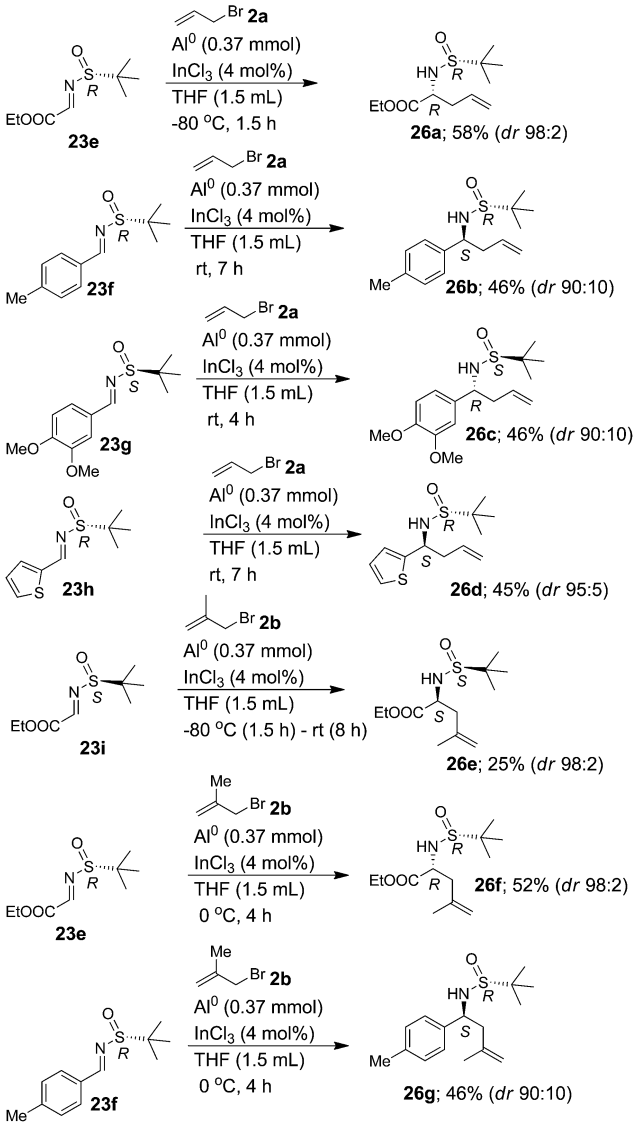
Scheme 9 $InCl_3$-catalyzed Al^0-based stereoselective addition to *N*-aryl α-imino ester **23a**, **23d**. The α-imino esters **23a**, **23d**, were prepared separately and then the corresponding α-imino esters **23a**, **23d** were treated with **2d** or **2f** or **2h**, Al^0 and $InCl_3$ in one pot.

Then, we attempted the addition of γ-substituted allylic halides to *N*-aryl α-imino esters and the construction of γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives bearing two contiguous stereocenters (Scheme 9). The addition of crotyl bromide (**2h**) or cyclohexenyl bromide (**2f**) to α-imino ester **23a** in the presence of $InCl_3$ and Al^0 powder in one pot gave the products, γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives **25a** (yield of 64%, *dr* 60 : 40) and **25b** (yield of 70%, *dr* 65 : 35). In these cases, the products **25a** and **25b** were obtained with a low diastereoselectivity and this may be because of the involvement of a less rigid transition state (TS) under the present experimental conditions involving the combination of $InCl_3$ and Al^0. However, the addition of α-imino esters **23a**, **23d** to cinnamyl bromide (**2d**), $InCl_3$ and Al^0 powder in one pot gave γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives **25c** (yield of 68%, *dr* 90 : 10) and **25d** (yield of 60%, *dr* 85 : 15) with very good diastereoselectivity (Scheme 9).

Additionally, we also tested the combination of $InCl_3$ and Al^0 for the stereoselective addition of allylmetals to a series of chiral *N*-*tert*-butylsulfinyl imino systems **23e–i**, prepared from the condensation of ethyl glyoxal or aromatic aldehydes and (*R*)-*N*-*tert*-butylsulfinyl amine or (*S*)-*N*-*tert*-butylsulfinyl amine. The addition reaction of various chiral imino systems including imino esters **23e–i** to a THF solution of allylmetal reagent prepared separately from allyl bromide and $InCl_3/Al^0$ successfully gave the γ,δ-unsaturated *N*-*tert*-butylsulfinyl α-amino acid derivatives **26a**, **26e**, **26f** and homoallylic amines **26b–d**, **26g** with very high diastereoselectivity (Scheme 10).

Stereochemistry

The stereochemistry of the compound **3g** prepared in this research was unequivocally confirmed based on the X-ray structure analysis (Fig. 1). The stereochemistry of other products **3a–l**,[16b] **3p**,[16b] **3q**,[16b] **6a**, **6b**,[16b] **4a**,[16b] and **25a–d** (ref. 18a) obtained in this research using the Al/$InCl_3$ system was assigned by comparing their spectral data with our previously published work,[16b,18a] where the stereochemistry and structure of various compounds have been already unambiguously confirmed on the basis of X-ray structure analysis.



Scheme 10 In the reaction involving the preparation of **26a**, the reaction was performed in one pot by treating **23e** (0.25 mmol), $InCl_3$/Al^0 and **2a** (2 equiv.). In the reactions involving the preparation of **26b–g**, the reactions were performed by treating **23e–i** (0.25 mmol) with a THF solution of allylmetal reagent prepared separately.

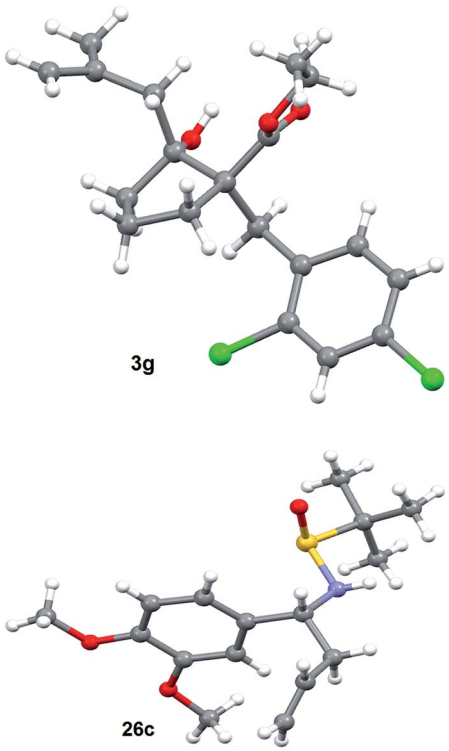
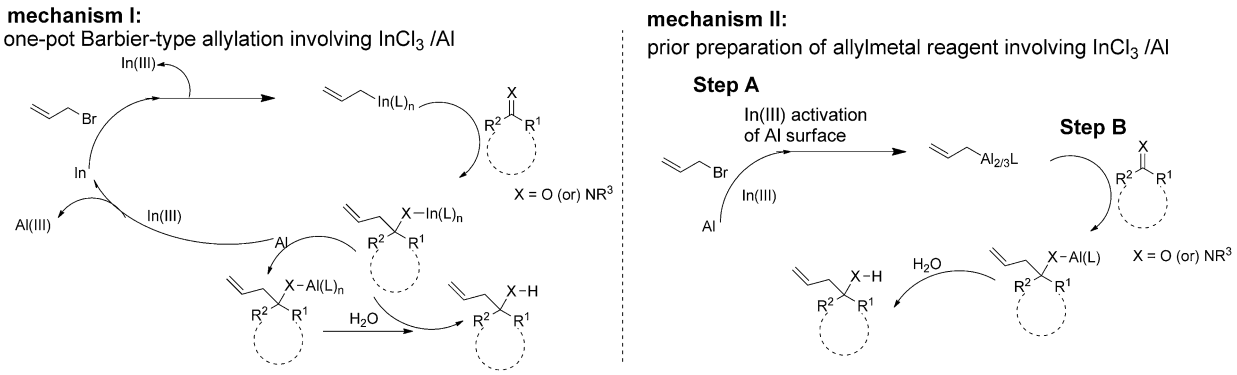


Fig. 1 X-ray structures of compounds **3g** and **26c**.

The compound (*R*)-2-methyl-*N*-((*S*)-1-(*p*-tolyl)but-3-en-1-yl) propane-2-sulfinamide (**26b**) obtained in this research was previously reported in the literature.[20f] We have prepared the compound **26b** using the procedure reported by Sun *et al.*[20f] and recorded its specific rotation ($[\alpha]_D^{28} = -91.7$ (*c* 0.024, DCM). The spectral data of compound **26b** obtained in this work using the Al/$InCl_3$ system was found to be similar to the spectral data of **26b** reported in the literature.[20f] Next, we recorded the specific rotation of the compound **26b** prepared using the Al/$InCl_3$ system $[\alpha]_D^{28} = -91.7$ (*c* 0.024, DCM). Since the spectral data as well as the specific rotation of the compound **26b** prepared using the Al/$InCl_3$ system and the reported method are similar, the stereochemistry of compound **26b** has been assigned as reported in the literature.[20f] Additionally, the compound **26d** has also been reported in the literature.[20f] Because the compounds **26d** and **26g** were also assembled in a similar manner to **26b** and based on the observed very high diastereoselectivity, the stereochemistry of compounds **26d** and **26g** was assigned after assigning the stereochemistry of **26b**. In this way, the stereochemistry of the product (*S*)-*N*-((*R*)-1-(3,4-dimethoxyphenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (**26c**) which is not reported in the literature was unambiguously established from the single crystal X-ray structure analysis (Fig. 1). Similarly, the compound (*R*)-ethyl 2-((R)-1,1-dimethylethylsulfinamido)pent-4-enoate (**26a**) obtained in this work was reported in the literature by the same group (Sun *et al.*)[20f] as discussed previously. The stereochemistry of compound **26a** has been assigned on the basis of the similarity of the spectral data pattern of compound **26a** obtained using the Al/$InCl_3$ system and the results in the literature.[20f] Consequently, because the compounds **26e** (starting from (*S*)-ethyl 2-((*tert*-butylsulfinyl)imino)acetate) and **26f** (starting from (*R*)-ethyl 2-((*tert*-butylsulfinyl)imino)acetate) were also assembled in a similar manner to **26a** and based on the very high diastereoselectivity observed and the similarity in their spectral data pattern, the stereochemistry of compounds **26e** and **26f** was assigned after assigning the stereochemistry of **26a**. Furthermore, the compounds **26e** ($[\alpha]_D^{28} = +25.0$ (*c* 0.024, DCM)) and **26f** ($[\alpha]_D^{26} = -25.0$ (*c* 0.024, DCM)) are enantiomers and their specific rotational values were found to have the opposite sign, which further clearly validated the assigned stereochemistry and revealed that the allylation of the compounds **23i** and **23e** is highly stereoselective.

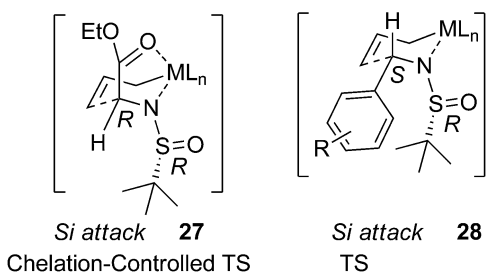
The preparation as well as stereochemistry of the compounds **26a** and **26b** are reported by Sun *et al.* using the corresponding imines **23e** and **23f**.[20f] Although the imine



Scheme 11 Plausible mechanism for the indium-catalyzed Al-based addition to carbonyl- and imino compounds.[12,13,18c–l]

systems **23e** and **23f** have been prepared using the same chiral amine ((R)-*N*-*tert*-butylsulfinyl amine), the configuration at the homoallyic chiral carbon in the corresponding products, *e.g.*, **26a** and **26b**, is opposite. The reason for this may be that the allylation of **23e** is proceeding *via* a well-known chelation controlled TS model[18a] **27** (Scheme 12) comprising an ester group, thereby giving the compound **26a** which has the opposite stereochemistry when compared to the product **26b** where there would not be assistance from chelation. Presumably, the aryl group, being a relatively bulky group, occupies the equatorial position in the six-membered cyclic TS[18a] **28**, thereby giving the compound **26b**.

In agreement with reports in the literature, in which the mechanism of generation of the allylmetal reagent from the $InCl_3/Al^0$ system is proposed,[12,13,18c–l] plausible mechanisms for the allylation of prostereogenic α,α-disubstituted cycloalkanones and imino compounds using the $InCl_3/Al^0$ system are proposed in Scheme 11. The involvement of both types of mechanisms, such as mechanism I and mechanism II, is highly possible.[13] For example, the substrate **1a** or **1b** (Tables 1 and 2) was reacted with allyl bromide, Al^0 and a catalytic amount of $InCl_3$ or In^0 in one pot. Perhaps, in this case, the allylation could be proceeding *via* allylic indium generated *in situ* involving the mechanism I.[13] However, in some cases we prepared the allylmetal reagent separately from allyl bromide, Al^0 and a catalytic amount of $InCl_3$ and then it was treated with imines. For example, the imino compounds **15a–f** (Schemes 6–10) were treated with a THF solution of allylmetal reagent prepared from allyl bromide, Al^0 and a catalytic amount of $InCl_3$. In these cases, perhaps, the allylation could be proceeding *via* mechanism II, as it is also proposed in the literature that catalytic amounts of $InCl_3$ activate the Al surface thereby leading to the formation of an allylmetal reagent.[13a,e,f,k] In view of these points, we also believe that in our reactions, the allylation reaction proceeds through mechanism II by involving an allylic aluminium reagent as an intermediate and $InCl_3$ may be acting as an activator.[12,13a,e,f,k]



Scheme 12 Plausible transition states (TS) for the stereoselectivity observed.

Conclusion

In summary, we have demonstrated the use of a catalytic amount of $InCl_3$ in combination with Al^0 powder for the diastereofacial selective allylation of prostereogenic α,α-disubstituted (hindered) cycloalkanones and the stereoselective construction of a stereoarray having consecutively attached tertiary carbinol- and an all carbon-based stereocenter in functionalized carbocyclic compounds. The allylation of various 2-substituted-2-carbethoxycyclopentanones gave the corresponding products with an excellent diastereoselectivity and, the allylation of various 2-substituted-2-carbethoxycyclohexanones gave the corresponding products with low diastereoselectivity. We have also reported the C–C bond forming protocol and the synthesis of homoallylic amines *via* the allylation of imino (C═N) functional groups using a catalytic amount of $InCl_3$ in combination with Al^0 powder. For the addition of γ-substituted allylic halides to α-imino esters low to very good diastereoselectivity was obtained. The allylation of chiral *N*-*tert*-butylsulfinyl imino systems including α-imino esters gave allylated products with an excellent diastereoselectivity. Considering that the aluminium metal is relatively inexpensive and less toxic when compared to other metals, further work and developments are anticipated, which will prove the effectiveness of the combination of In and Al as an efficient alternative for performing Barbier-type allylation reactions.

Experimental section

General considerations

Melting points are uncorrected. Fourier-transform infrared (FT-IR) spectra were recorded using thin films or KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 400 MHz and

100 MHz spectrometers, respectively. Column chromatography was carried out on silica gel (100–200 mesh) or neutral alumina. Thin layer chromatography (TLC) was performed on silica plates or neutral alumina and components were visualized by observation under iodine. Anhydrous solvents were prepared using standard drying methods. Reactions were carried out in anhydrous solvents under a nitrogen atmosphere where required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask with the help of a syringe. Yields were not optimized and the ratios of diastereomers were determined from the NMR spectra of crude reaction mixtures or after isolation. The ratio of diastereoselectivity (*dr* 98 : 2) refers to the predominant presence of the major diastereomer and only traces of the corresponding minor isomer in the NMR spectrum of the crude reaction mixture. All the starting materials were prepared using standard procedures previously reported in the literature.

Procedure A. General Procedure for the preparation of compounds **3a–3q**, **4a**, **5b**, **6a**, **6b** and **9**/**10**. To a solution of cyclic ketone (0.5 mmol) in anhydrous THF (1.5 mL) were added $InCl_3$ (1–2 mol%), Al powder (0.55 mmol) and allyl/propargyl bromide (1.0 mmol) under a nitrogen atmosphere and this reaction mixture was stirred at room temperature for an appropriate time as indicated in the respective Tables/Schemes. After the completion of the reaction, the reaction mixture was quenched by adding water (2 mL). The reaction mixture was transferred into a separating funnel and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture was by column chromatography on silica gel (EtOAc/hexane as eluent) to give the corresponding product (see the corresponding Tables/Schemes for specific reactions).

Procedure B. General Procedure for the preparation of compounds **24a**, **24b**, **25a–d** and **26a**. To a solution of $InCl_3$ (3–4 mol%), Al powder (0.75 mmol) and allyl bromide/prenyl bromide/crotyl bromide/cinnamyl bromide/propargyl bromide/cyclohexenyl bromide (1.0 mmol) in anhydrous THF (1.5 mL), the corresponding imine (0.5 mmol) was added at an appropriate temperature as indicated in the corresponding Tables/Schemes and the reaction mixture was stirred for an appropriate time under a nitrogen atmosphere as mentioned in the respective Tables/Schemes. After this period, the reaction mixture was quenched by adding water (2 mL). The reaction mixture was transferred into a separating funnel and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the corresponding product (see the corresponding Tables/Schemes for specific reactions).

Procedure C. General Procedure for the preparation of compounds **8a–c**, **16a–h**, **20–22**, **24c**, **24d** and **26b–g**. To a solution of $InCl_3$ (3–4 mol%) and Al powder (0.75 mmol) in anhydrous THF (1.5 mL) was added allyl bromide/prenyl bromide/crotyl bromide/cinnamyl bromide/propargyl bromide/cyclohexenyl bromide (1.0 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature. After 15 min the corresponding imine/carbonyl compound (0.5 mmol) was added to the above reaction mixture at a specific temperature for an appropriate time as indicated in the respective Tables/Schemes. After this period, the reaction mixture was quenched by adding water (2 mL). The reaction mixture was transferred into a separating funnel and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the product (see the corresponding Tables/Schemes for specific reactions).

Procedure D. Synthesis of triazole **11**. To the solution of a mixture of compounds **9**/**10** (0.5 mmol), $CuSO_4 \cdot 5H_2O$ (30 mol%) and (+)-sodium L-ascorbate in THF–H_2O (2 : 1, 6 mL) was added benzyl azide (0.75 mmol) and the reaction mixture was stirred overnight at room temperature. After the completion of the reaction, the reaction mixture was transferred into a separating funnel and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave product **11**.

Procedure E. Preparation of compound **12**. To the solution of a mixture of compounds **9**/**10** (0.5 mmol) in dimethyl sulfoxide (DMSO, 3 mL) was added $Cu(OAc)_2$ (40 mol%) and the reaction mixture was stirred under an open atmosphere for 24 h at 105 °C. After completion of the reaction, the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane as eluent) gave the product **12**.

Copies of the NMR spectra of all the known and unknown compounds reported in this work can be found in the ESI.† In Table 2, except for compounds **3e**, **3g**, **3h**, **3m**, **3o** and **3q**, all the other compounds were found in the literature and their spectral data were compared with the spectral data reported in our previous research.[16b] The spectral data of the known compounds **8a**,[19a] **8b**,[19b] **9**/**10**,[16b] **16a**,[20a] **16b**,[20b] **16d**,[20c] **22**,[20d] **24a**,[2f] **25a**,[18a] **25b**,[20e] **25c**,[18a] **25d**,[18a] **26a**,[20f] **26b**,[20f] and **26d** (ref. 20f) were compared with the spectral data reported in the literature. The compound **5a** could not be isolated in pure form. The compound **8b** was obtained as a mixture of diastereomers (*dr* 90 : 10).

Ethyl (1*S,2*S**)-2-allyl-2-hydroxy-1-(4-nitrobenzyl)cyclopentanecarboxylate (3e).** Following the general procedure A described previously, **3e** (*anti*, major isomer) was obtained after purification by silica gel column chromatography (EtOAc : hexane = 07 : 93) as a semi-solid (126 mg, yield: 76%); FT-IR (neat): 3543, 1716, 1519 and 1347 cm^{-1}; ^{1}H-NMR (400 MHz, deuterated chloroform ($CDCl_3$)): δ 8.12 (d, 2H, J = 8.6 Hz), 7.32 (d, 2H, J = 8.6 Hz), 6.00–5.90 (m, 1H), 5.24–5.15 (m, 2H), 4.17–4.09 (m, 2H), 3.51 (d, 1H, J = 13.5 Hz), 2.91 (d, 1H, J = 13.5 Hz), 2.34–2.23 (m, 2H), 2.14 (br s, 1H), 2.01–1.75 (m, 6H), 1.24 (t, 3H, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.7, 146.9, 146.7, 133.5, 130.7, 123.3, 119.4, 83.1, 61.6, 60.8, 42.0, 37.8, 34.8, 29.9, 18.6, 14.2; high-resolution mass spectroscopy –

electrospray ionisation (HRMS (ESI)): calculated for $C_{18}H_{23}NNaO_5$ $[M + Na]^+$ 356.1474, actual 356.1441.

Ethyl (1*S,2*S**)-1-(2,4-dichlorobenzyl)-2-hydroxy-2-(2-methylallyl)cyclopentanecarboxylate (3g).**[21] Following the general procedure A described previously, **3g** (*anti*, major isomer) was obtained after purification by silica gel column chromatography (EtOAc : hexane = 06 : 94) as a white solid (122 mg, yield: 66%); mp = 80–82 °C; FT-IR (KBr): 3500, 1716, 1473 and 889 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (d, 1H, $J = 2.2$ Hz), 7.14 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz), 7.07 (d, 1H, $J = 8.4$ Hz), 4.97 (s, 1H), 4.80 (s, 1H), 4.18 (q, 2H, $J = 7.1$ Hz), 3.37 (d, 1H, $J = 14.5$ Hz), 3.23 (d, 1H, $J = 14.5$ Hz), 2.28 (s, 1H), 2.21 (d, 1H, $J = 3.8$ Hz), 2.07–1.64 (m, 6H), 1.88 (s, 3H), 1.26 (t, 3H, $J = 7.1$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.6, 142.6, 136.0, 135.4, 132.6, 131.5, 129.4, 126.9, 115.3, 83.5, 61.6, 60.8, 44.8, 34.2, 33.6, 28.5, 24.5, 18.6, 14.2; HRMS (ESI): calculated for $C_{19}H_{25}Cl_2O_3$ $[M + H]^+$ 371.1181, actual 371.1001.

Ethyl (1*R,2*S**)-2-hydroxy-2-(2-methylallyl)-1-pentylcyclopentanecarboxylate (3h).** Following the general procedure A described previously, **3h** (*anti*, major isomer) was obtained after purification by silica gel column chromatography (EtOAc : hexane = 05 : 95) as a colourless liquid (119 mg, yield: 78%); FT-IR (neat): 3534, 2958, 1721 and 1463 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.90 (s, 1H), 4.73 (s, 1H), 4.23–4.09 (m, 2H), 2.20–2.06 (m, 3H), 2.05 (s, 1H), 1.99–1.84 (m, 2H), 1.82 (s, 3H), 1.77–1.62 (m, 4H), 1.44–1.37 (m, 1H), 1.33–1.24 (m, 5H), 1.28 (t, 3H, $J = 7.1$ Hz), 1.07–1.00 (m, 1H), 0.87 (t, 3H, $J = 6.8$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.9, 142.9, 1144.9, 82.6, 60.9, 60.3, 44.9, 34.5, 32.5, 32.0, 29.8, 25.0, 24.5, 22.5, 18.8, 14.3, 14.0; HRMS (ESI): calculated for $C_{17}H_{30}NaO_3$ $[M + Na]^+$ 305.2093, actual 305.2059.

3-(2-Allyl-2-hydroxy-1-methylcyclohexyl)propane nitrile (3m). Following the general procedure A described previously, **3m** was obtained as a mixture of diastereomers (*dr* 60 : 40) after purification by silica gel column chromatography (EtOAc : hexane = 20 : 80) as a light yellow liquid (62 mg, yield: 60%); FT-IR (neat): 3512, 2939, 2246 and 1462 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.91 5.80 (m, 1H), 5.21 5.10 (m, 2H), 2.45 2.19 (m, 4H), 2.07 1.71 (m, 2H), 1.60 1.37 (m, 8H), 0.94 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 133.8, 133.7, 121.2, 120.8, 119.7, 119.3, 75.0, 74.9, 39.9, 39.7, 39.4, 38.8, 33.6, 32.9, 32.6, 32.6, 32.2, 22.0, 21.5, 21.0, 21.0, 20.6, 18.8, 12.6; HRMS (ESI): calculated for $C_{13}H_{21}NNaO$ $[M + Na]^+$ 230.1521, actual 230.1363. NMR values are given for both the diastereomers.

Ethyl 2-(4-bromobenzyl)-3-hydroxy-2,3-dimethylhex-5-enoate (3o). Following the general procedure A described previously, **3o** was obtained as a mixture of diastereomers (*dr* 55 : 45) after purification by silica gel column chromatography (EtOAc : hexane = 07 : 93) as a colourless liquid (144 mg, yield: 81%); FT-IR (neat): 3486, 1714, 1488 and 1012 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (d, 2H, $J = 8.0$ Hz), 6.97 (d, 2H, $J = 8.0$ Hz), 6.06–5.91 (m, 1H), 5.17–5.03 (m, 2H), 4.06–3.95 (m, 2H), 3.83 (s, 1H), 3.51 (d, 1H, $J = 13.2$ Hz), 2.58 (d, 1H, 13.2 Hz), 2.34 (dd, 1H, $J_1 = 13.9$ Hz, $J_2 = 8.2$ Hz), 2.17–2.09 (m, 1H), 1.18 (s, 3H), 1.12 (t, 3H, $J = 7.1$ Hz), 1.09 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.2, 176.8, 137.0, 136.8, 134.3, 134.1, 132.0, 132.0, 131.1, 131.1, 120.5, 120.5, 118.0, 117.9, 76.0, 75.3, 61.0, 55.5, 55.0, 43.6, 40.4, 39.3, 38.8, 23.7, 20.9, 17.5, 17.4, 14.0, 13.9; HRMS (ESI): calculated for $C_{17}H_{23}BrNaO_3$ $[M + Na]^+$ 377.0728, actual 377.0696. NMR values are given for both the diastereomers.

Ethyl (1*S,2*S**)-2-allyl-1-benzhydryl-2-hydroxycyclopentanecarboxylate (3q).** Following the general procedure A described previously, **3q** (*anti*, major isomer) was obtained after purification by silica gel column chromatography (EtOAc : hexane = 05 : 95) as a white solid (158 mg, yield: 87%); mp = 80–82 °C; FT-IR (KBr): 3528, 1722, 1495 and 704 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 2H, $J = 7.1$ Hz), 7.42 (d, 2H, $J = 7.4$ Hz), 7.29–7.13 (m, 6H), 5.97–5.87 (m, 1H), 5.18–5.07 (m, 2H), 5.09 (s, 1H), 3.95–3.86 (m, 2H), 2.79–2.65 (m, 2H), 2.30 (dd, 1H, $J_1 = 14.1$ Hz, $J_2 = 8.1$ Hz), 2.21 (s, 1H), 2.18–2.12 (m, 1H), 1.76–1.12 (m, 4H), 0.93 (t, 3H, $J = 7.1$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.8, 143.8, 142.7, 133.8, 130.9, 129.1, 128.1, 128.1, 126.5, 126.1, 118.7, 84.0, 64.2, 60.6, 53.2, 43.0, 34.0, 28.4, 18.7, 13.6; HRMS (ESI): calculated for $C_{24}H_{28}NaO_3$ $[M + Na]^+$ 387.1936, actual 387.1911. This compound was isolated together with its minor isomer.

Ethyl 2-allyl-1-(2-ethoxy-2-oxoethyl)-2-hydroxycyclohexanecarboxylate (5b). Following the general procedure A described previously, **5b** was obtained as a pure compound after purification by silica gel column chromatography (EtOAc : hexane = 05 : 95) as a colourless liquid (39 mg, yield: 26%); FT-IR (neat): 3512, 1737, 1715 and 1176 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.96–5.86 (m, 1H), 5.12–5.05 (m, 2H), 4.29–4.15 (m, 2H), 4.10 (q, 2H, $J = 7.2$ Hz), 3.86 (s, 1H), 2.79 (d, 1H, $J = 15.0$ Hz), 2.56 (d, 1H, $J = 15.0$ Hz), 2.52 (dd, 1H, $J_1 = 13.7$ Hz, $J_2 = 5.6$ Hz), 2.25–2.16 (m, 2H), 1.74–1.34 (m, 7H), 1.30 (t, 3H, $J = 7.1$ Hz), 1.24 (t, 3H, $J = 7.1$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.9, 171.3, 133.8, 117.8, 74.3, 61.1, 60.5, 52.8, 39.4, 38.5, 33.1, 31.6, 21.8, 21.7, 14.1, 14.0; HRMS (ESI): calculated for $C_{16}H_{26}O_5Na$ $[M + Na]^+$ 321.1678, actual 321.1682.

1,2-Diallyl-1,2-dihydroacenaphthylene-1,2-diol (8c). Following the general procedure C described previously, **8c** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 20 : 80) as a white solid (65 mg, yield: 98%); mp = 143–145 °C; FT-IR (KBr): 3362, 1638, 1374 and 1057 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 2H, $J = 8.3$ Hz), 7.58 (dd, 2H, $J_1 = 8.3$ Hz, $J_2 = 6.9$ Hz), 7.42 (d, 2H, $J = 6.9$ Hz), 5.90–5.79 (m, 2H), 5.20–5.14 (m, 4H), 2.88–2.82 (m, 2H), 2.69 (s, 2H), 2.60 (dd, 2H, $J_1 = 13.9$ Hz, $J_2 = 7.9$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.7, 134.3, 134.1, 130.6, 128.1, 124.6, 119.5, 119.5, 86.4, 43.8; HRMS (ESI): calculated for $C_{18}H_{17}O_2$ $[M - H]^+$ 265.1229, actual 265.1337.

Ethyl (1*S,2*S**)-1-benzyl-2-((1-benzyl-1*H*-1,2,3-triazol-5-yl)methyl)-2-hydroxycyclopentanecarboxylate (11).** Following the general procedure D described previously, **11** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 30 : 70) as a brownish yellow solid (124 mg, yield: 59%); mp = 83–85 °C; FT-IR (KBr): 3409, 1716, 1454 and 703 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.38–7.35 (m, 3H), 7.28–7.19 (m, 5H), 7.12–7.10 (m, 2H), 5.52 (s, 2H), 4.14–4.00 (m, 2H), 3.79 (br s, 1H), 3.26 (d, 1H, $J = 13.5$ Hz), 2.98 (d, 1H, $J = 18.7$ Hz), 2.95 (d, 1H, $J = 18.7$ Hz), 2.80 (d, 1H, $J = 13.5$ Hz), 2.06–1.70 (m, 6H), 1.18 (t, 3H, $J = 7.1$ Hz); ^{13}C-NMR (100

MHz, $CDCl_3$): δ 175.4, 144.8, 138.6, 134.8, 129.9, 129.1, 128.7, 128.1, 128.0, 126.3, 122.7, 83.2, 61.9, 60.6, 54.1, 38.0, 35.5, 33.2, 30.0, 18.5, 14.1; HRMS (ESI): calculated for $C_{25}H_{29}N_3NaO_3$ $[M + Na]^+$ 442.2107, actual 442.2104. The stereochemistry of the products **9**/**10** had been reported previously[16b] and based on this the stereochemistry of **11** was assigned.

Preparation of compound 12. Following the general procedure E described previously, **12** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 25 : 75) as a white solid (175 mg, yield: 60%); mp = 117–119 °C; FT-IR (KBr): 3493, 2979, 1716 and 738 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26–7.22 (m, 6H), 7.14–7.12 (m, 4H), 4.16–4.08 (m, 4H), 3.42 (d, 2H, J = 13.6 Hz), 2.81 (d, 2H, J = 13.6 Hz), 2.62 (d, 2H, J = 16.8 Hz), 2.56 (d, 2H, J = 16.8 Hz), 2.41 (s, 2H), 2.11–1.68 (m, 12H), 1.24 (t, 6H, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.6, 138.1, 129.9, 128.2, 126.5, 82.5, 74.0, 67.8, 61.1, 60.8, 37.8, 35.8, 29.6, 29.6, 18.1, 14.1; HRMS (ESI): calculated for $C_{36}H_{42}NaO_6$ $[M + Na]^+$ 593.2879, actual 593.2894. The stereochemistry of the products **9**/**10** had been reported previously[16b] and based on this the stereochemistry of **12** was assigned.

3,4-Dichloro-*N*-(1-(3,4-dimethoxyphenyl)but-3-en-1-yl)aniline (16c). Following the general procedure C described previously, **16c** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 15 : 85) as a light yellow liquid (163 mg, yield: 93%); FT-IR (neat): 3385, 1597, 1514 and 1027 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10 (d, 1H, J = 8.7 Hz), 6.89 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 6.86–6.84 (m, 2H), 6.60 (d, 1H, J = 2.7 Hz), 6.35 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.7 Hz), 5.81–5.71 (m, 1H), 5.24–5.17 (m, 2H), 4.30–4.23 (m, 1H), 4.23 (s, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 2.64–2.45 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 149.3, 148.1, 146.9, 135.0, 134.3, 132.5, 130.4, 119.9, 118.7, 118.2, 114.8, 113.1, 111.3, 109.1, 56.9, 55.9, 55.9, 43.2; HRMS (ESI): calculated for $C_{18}H_{20}Cl_2NO_2$ $[M + H]^+$ 352.0871, actual 352.0601.

***N*-((4-Bromophenyl)(cyclohex-2-en-1-yl)methyl)-4-methylaniline (16e).** Following the general procedure C described previously, **16e** was obtained as a mixture of diastereomers (*dr* 70 : 30) after purification by silica gel column chromatography (EtOAc : hexane = 05 : 95) as a light yellow liquid (129 mg, yield: 73%); FT-IR (neat): 3414, 1618, 1519 and 806 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.48 (d, 2H, J = 8.5 Hz), 7.26 (d, 2H, J = 8.5 Hz), 6.95 (d, 2H, J = 8.1 Hz), 6.43 (d, 2H, J = 8.1 Hz), 5.98–5.91 (m, 1H), 5.60 (dd, 1H, J_1 = 10.2 Hz, J_2 = 1.5 Hz), 4.30–4.27 (m, 1H), 4.04 (s, 1H), 2.24 (s, 3H), 2.08 (s, 2H), 1.85–1.80 (m, 2H), 1.61–1.48 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.4, 145.0, 142.0, 141.6, 132.5, 131.5, 131.0, 130.8, 129.7, 129.6, 128.9, 128.8, 128.7, 126.8, 126.3, 125.8, 120.5, 113.7, 113.1, 61.8, 61.2, 43.1, 42.8, 27.6, 25.3, 25.2, 23.7, 21.9, 21.8, 20.4; HRMS (ESI): calculated for $C_{20}H_{23}BrN$ $[M + H]^+$ 356.1014, actual 356.0970. NMR values are given for both the isomers.

***N*-[(4-Chlorophenyl)(cyclohex-2-en-1-yl)methyl]-3,4-dimethylaniline (16f).** Following the general procedure C described previously, **16f** was obtained as a mixture of diastereomers (*dr* 70 : 30) after purification by silica gel column chromatography (EtOAc : hexane = 10 : 90) as a reddish brown liquid (130 mg, yield: 80%); FT-IR (neat): 3418, 1617, 1510 and 801 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37–7.35 (m, 4H), 6.92 (d, 1H, J = 7.9 Hz), 6.42 (s, 1H), 6.28–6.27 (m, 1H), 5.98 (d, 1H, J = 9.6 Hz), 5.64–5.57 (m, 1H), 4.34–4.31 (m, 1H), 4.03 (s, 1H), 2.64 (s, 1H), 2.22 (s, 3H), 2.19 (s, 3H), 2.10 (s, 2H), 1.87–1.54 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.9, 145.6, 141.7, 141.2, 137.3, 137.2, 132.3, 131.4, 130.8, 130.3, 130.2, 129.0, 128.6, 128.4, 128.3, 125.9, 125.6, 125.1, 115.6, 114.9, 110.8, 110.3, 61.7, 61.1, 43.2, 42.9, 27.7, 25.3, 25.3, 23.7, 22.0, 21.8, 20.1, 18.7; HRMS (ESI): calculated for $C_{21}H_{25}ClN$ $[M + H]^+$ 326.1676, actual 326.1646. NMR values are given for both the isomers.

***N*-(1-(4-Bromophenyl)but-3-en-1-yl)-O-methylhydroxylamine (16g).** Following the general procedure C described previously, **16g** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 07 : 93) as a colourless liquid (96 mg, yield: 75%); FT-IR (KBr): 1639, 1485, 1104 and 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 2H, J = 8.4 Hz), 7.19 (d, 2H, J = 8.4 Hz), 5.81–5.70 (m, 1H), 5.09–5.04 (m, 2H), 4.18–4.14 (m, 1H), 3.23 (s, 3H), 2.60–2.36 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 140.8, 134.3, 131.5, 128.5, 121.4, 117.3, 83.0, 56.7, 42.4. The NH proton could not be detected in this compound.

***N*-(1-(4-Bromophenyl)but-3-en-1-yl)-*N*-methylhydroxylamine (16h).** Following the general procedure C described previously, **16h** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 10 : 90) as a yellowish brown solid (63 mg, yield: 50%); mp = 72–74 °C; FT-IR (KBr): 3224, 1487, 1011 and 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.48 (d, 2H, J = 8.4 Hz), 7.19 (d, 2H, 8.4 Hz), 5.64–5.54 (m, 1H), 5.03–4.96 (m, 2H), 3.57 (dd, 1H, J_1 = 9.2 Hz, J_2 = 5.0 Hz), 2.88–2.81 (m, 1H), 2.57–2.49 (m, 1H), 2.54 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 134.6, 131.5, 130.4, 121.6, 117.3, 73.3, 46.0, 38.1; HRMS (ESI): calculated for $C_{11}H_{15}BrNO$ $[M + H]^+$ 256.0337, actual 256.0155. The OH proton could not be detected in this compound.

3-Allyl-3-(phenylamino)indolin-2-one (20). Following the general procedure C described previously, **20** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 20 : 80) as a white solid (106 mg, yield: 80%); mp = 163–165 °C; FT-IR (KBr): 3312, 1603, 1716 and 1470 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.29–7.23 (m, 2H), 7.07–6.98 (m, 3H), 6.90 (d, 1H, J = 7.7 Hz), 6.69–6.65 (m, 1H), 6.32 (dd, 1H, J_1 = 8.7 Hz, J_2 = 1.0 Hz), 5.86–5.76 (m, 1H), 5.29–5.22 (m, 2H), 4.73 (s, 1H), 2.80 (dd, 1H, J_1 = 13.3 Hz, J_2 = 7.1 Hz), 2.66 (dd, 1H, J_1 = 13.3 Hz, J_2 = 7.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 181.0, 145.2, 139.8, 130.3, 129.1, 129.0, 124.0, 123.0, 121.2, 118.8, 114.4, 111.0, 64.3, 44.7; HRMS (ESI): calculated for $C_{17}H_{16}N_2NaO$ $[M + Na]^+$ 287.1160, actual 287.1125.

Ethyl 2-(2-tosylhydrazinyl)pent-4-enoate (21). Following the general procedure C described previously, **21** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 30 : 70) as yellowish thick liquid (31 mg, yield: 20%); FT-IR (neat): 3300, 3249, 1727 and 738 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.82 (d, 2H, J = 8.3 Hz), 7.33 (d, 2H, J = 8.0 Hz), 6.36 (s, 1H), 5.71–5.61 (m, 1H), 5.10–5.06 (m, 2H), 4.20 (q, 2H, J = 7.2 Hz), 3.92 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.9 Hz), 3.64–3.59 (m, 1H), 2.45 (s, 3H), 2.44-2.32 (m, 2H), 1.29 (t, 3H, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.4, 144.0, 135.0, 132.6, 129.5, 128.2, 118.5, 62.9, 61.4, 34.8, 21.6, 14.2; HRMS (ESI): calculated for $C_{14}H_{20}N_2NaO_4S$ $[M + Na]^+$ 335.1041, actual 335.1013.

Ethyl 2-((4-methoxyphenyl)amino)pent-4-ynoate (24b). Following the general procedure B described previously, **24b** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 20 : 80) as a reddish black thick liquid (71 mg, yield: 58%); FT-IR (neat): 3286, 1738, 1514 and 1241 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.80 (d, 2H, J = 9.0 Hz), 6.67 (d, 2H, J = 9.0 Hz), 4.29–4.20 (m, 2H), 4.19 (t, 1H, J = 5.4 Hz), 3.77 (s, 3H), 2.78 (dd, 2H, J_1 = 5.4 Hz, J_2 = 2.6 Hz), 2.11 (t, 1H, J = 2.6 Hz), 1.33 (t, 3H, J = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2, 153.1, 140.1, 115.7, 114.9, 78.9, 71.6, 61.5, 56.3, 55.7, 22.9, 14.2; HRMS (ESI): calculated for $C_{14}H_{18}NO_3$ $[M + H]^+$ 248.1287, actual 248.1268. The NH proton could not be detected in this compound.

Ethyl 2-[(3,4-dimethylphenyl)amino]pent-4-ynoate (24c). Following the general procedure C described previously, **24c** was obtained after purification by neutral alumina column chromatography (EtOAc : hexane = 10 : 90) as a brownish black thick liquid (46 mg, yield: 38%); FT-IR (neat): 3391, 1738, 1510 and 1209 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.97 (d, 1H, J = 8.0 Hz), 6.53 (d, 1H, J = 2.4 Hz), 6.45 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.4 Hz), 4.29–4.24 (m, 3H), 2.79 (dd, 2H, J_1 = 5.1 Hz, J_2 = 2.7 Hz), 2,22 (s, 3H), 2.18 (s, 3H), 2.10 (t, 1H, J = 2.7 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.1, 144.1, 137.5, 130.4, 126.9, 115.9, 111.3, 78.9, 71.5, 61.5, 55.4, 22.9, 20.0, 18.8, 14.3; HRMS (ESI): calculated for $C_{15}H_{20}NO_2$ $[M + H]^+$ 246.1494, actual 246.1458. The NH proton could not be detected in this compound.

Ethyl 2-[(4-bromophenyl)amino]pent-4-ynoate (24d). Following the general procedure C described previously, **24d** was obtained after purification by neutral alumina column chromatography (EtOAc : hexane = 10 : 90) as a light yellow liquid (59 mg, yield: 40%); FT-IR (neat): 3392, 3295, 1737 and 651 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29 (d, 2H, J = 8.9 Hz), 6.55 (d, 2H, J = 8.9 Hz), 4.49 (s, 1H), 4.30–4.21 (m, 3H), 2.79 (dd, 2H, J_1 = 5.2 Hz, J_2 = 2.6 Hz), 2.11 (t, 1H, J = 2.6 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 145.1, 132.1, 115.4, 110.5, 78.6, 71.9, 61.8, 54.9, 22.7, 14.2; HRMS (ESI): calculated for $C_{13}H_{15}BrNO_2$ $[M + H]^+$ 296.0286, actual 296.0265.

(*S*)-*N*-((*R*)-1-(3,4-Dimethoxyphenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (26c).[21] Following the general procedure C described previously, **26c** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 90 : 10) as a white solid (36 mg, yield: 46%); $[\alpha]_D^{28}$ = +54.6 (c 0.044, DCM); mp = 103–105 °C; FT-IR (KBr): 3417, 1638, 1421 and 738 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.90 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.9 Hz), 6.86 (d, 1H, J = 1.9 Hz), 6.84 (d, 1H, J = 8.0 Hz), 5.81–5.70 (m, 1H), 5.22–5.17 (m, 2H), 4.44–4.40 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.68 (br s, 1H), 2.62–2.41 (m, 2H), 1.22 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.9, 148.4, 134.4, 134.1, 119.9, 119.2, 110.8, 110.3, 56.6, 55.8, 55.8, 55.5, 43.6, 22.6; HRMS (ESI): calculated for $C_{16}H_{26}NO_3S$ $[M + H]^+$ 312.1633, actual 312.1607.

Ethyl (*S*)-2-((*S*)-1,1-dimethylethylsulfinamido)-4-methylpent-4-enoate (26e). Following the general procedure C described previously, **26e** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 70 : 30) as a light yellow liquid (16 mg, yield: 25%); $[\alpha]_D^{28}$ = +25.0 (c 0.024, DCM); FT-IR (neat): 3402, 1738 and 1056 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.85 (s, 1H), 4.77 (s, 1H), 4.24 (q, 2H, J = 7.2 Hz), 4.11–4.04 (m, 2H), 2.54–2.38 (m, 2H), 1.76 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz), 1.25 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.2, 140.3, 114.6, 61.7, 56.2, 42.5, 22.6, 22.1, 14.1; HRMS (ESI): calculated for $C_{12}H_{24}NO_3S$ $[M + H]^+$ 262.1477, actual 262.1480.

Ethyl (*R*)-2-((*R*)-1,1-dimethylethylsulfinamido)-4-methylpent-4-enoate (26f). Following the general procedure C described previously, **26f** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 65 : 30) as a colourless liquid (34 mg, yield: 52%); $[\alpha]_D^{26}$ = −25.0 (c 0.024, DCM); FT-IR (neat): 3406, 1738 and 1054 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.85 (s, 1H), 4.77 (s, 1H), 4.24 (q, 2H, J = 7.1 Hz), 4.10–4.04 (m, 2H), 2.54–2.38 (m, 2H), 1.77 (s, 3H), 1.31 (t, 3H, J = 7.1 Hz), 1.25 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.2, 140.3, 114.6, 61.7, 56.2, 42.5, 22.6, 22.1, 14.1; HRMS (ESI): calculated for $C_{12}H_{24}NO_3S$ $[M + H]^+$ 262.1477, actual 262.1481.

(*R*)-2-methyl-*N*-((*S*)-3-methyl-1-(*p*-tolyl)but-3-en-1-yl)propane-2-sulfinamide (26g). Following the general procedure C described previously, **26g** was obtained after purification by silica gel column chromatography (EtOAc : hexane = 60 : 40) as a white solid (33 mg, yield: 47%); $[\alpha]_D^{28}$ = −87.5 (c 0.032, DCM); mp = 51–53 °C; FT-IR (KBr): 3414, 1645, 1063 and 738 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, 2H, J = 8.0 Hz), 7.17 (d, 2H, J = 7.8 Hz), 4.95 (s, 1H), 4.89 (s, 1H), 4.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 5.7 Hz), 3.73 (s, 1H), 2.44–2.35 (m, 2H), 2.36 (s, 3H), 1.81 (s, 3H), 1.21 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.2, 139.2, 137.3, 129.2, 127.4, 114.9, 55.6, 54.2, 48.0, 22.6, 21.8, 21.2; HRMS (ESI): calculated for $C_{16}H_{26}NOS$ $[M + H]^+$ 280.1735, actual 280.1707. This compound was isolated as a mixture of diastereomers and the NMR values are given for the major diastereomer.

Acknowledgements

This work was funded by IISER Mohali. We thank IISER Mohali for the use of their NMR, X-ray and HRMS facilities. We also thank the single crystal X-ray facility of the Department of Chemical Sciences, IISER Mohali. C. R. and N. A. Aslam thank the CSIR-UGC, New Delhi, for their SRF fellowships.

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