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An asymmetric nickel–chromium coupling toward the synthesis of Baylis–Hillman adducts

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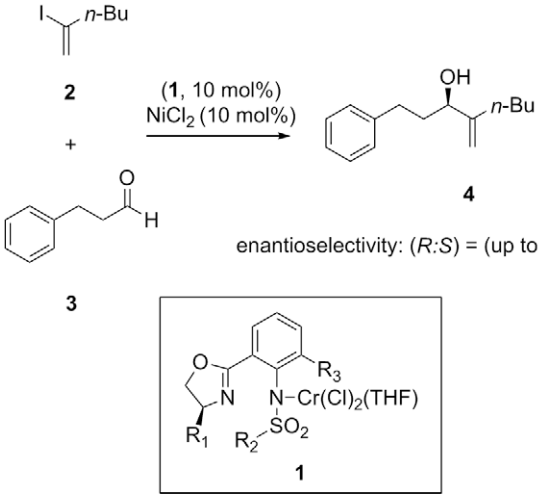
ABSTRACT

An asymmetric nickel–chromium coupling strategy has been employed in the generation of enantioenriched Baylis–Hillman adducts with selectivities reaching >90% ee and in fair to moderate yields (up to 65%) using a chiral sulfonamide ligand. The reaction conditions appear to show reasonable generality and are compatible with both aromatic and aliphatic aldehydes. Utilizing such a strategy not only allows for the preparation of products which contain substitution at the β-position on the olefin but also allows for the separation of olefin isomers in this transformation.

The Baylis–Hillman reaction represents one of many important carbon–carbon bond-forming reactions whose utility can be found in the synthesis of natural products and medicinally relevant compounds.[1] The significance of this transformation lies in the generation of densely functionalized carbon skeletons from the simple coupling of readily available α,β-unsaturated carbonyl compounds and aldehydes in the presence of a tertiary amine or phosphine catalyst. Traditionally, however, this intriguing reaction is often hindered by the lack of reactivity and scope of substrates efficient in this process. Despite recent developments in the generation of asymmetric catalysts which have resulted in some elegant examples of high yielding and highly enantioselective Baylis–Hillman products, the need for alternative methods for the preparation of these novel synthons is still of great interest.[2] In the context of the total synthesis of Luminacin D at Eisai Inc., the strategy toward the synthesis of fragment **A** consisted of a Baylis–Hillman synthon from which all stereocenters within this complex natural product are established (Scheme 1).[3] From these studies, we sought to probe the generality of using a nickel–chromium process to create these allylic alcohols. We report herein an asymmetric Nozaki–Hiyama–Kishi coupling aimed at the synthesis of enantioenriched Baylis–Hillman adducts of increased tolerance to substrate substitution and functionality.

Stimulated by the discovery of a catalytic nickel–chromium-mediated coupling, several research groups have recently disclosed a number of catalytic asymmetric protocols.[4] Included among those expanding the frontiers in this area of interest, Kishi and co-workers have reported that chiral sulfonamide chromium complex **1** under catalytic conditions in the presence of vinyl iodide **2** and aldehyde **3** affords allylic alcohol **4** in good yields and enantioselectivity (Eq. 1).[5] Inspired by these results, we were attracted to the feasibility of applying these conditions to α-halo-α,β-unsaturated carbonyl compounds in an effort to furnish the desired Baylis–Hillman adducts.



In preliminary experiments, it was determined that under stoichiometric conditions, coupling of methyl α-bromoacrylate **5** and aldehyde **6** using $CrCl_2$, $NiCl_2$, and sulfonamide ligand **7** in THF afforded the desired product **8** in 30% yield and 87% enantiomeric

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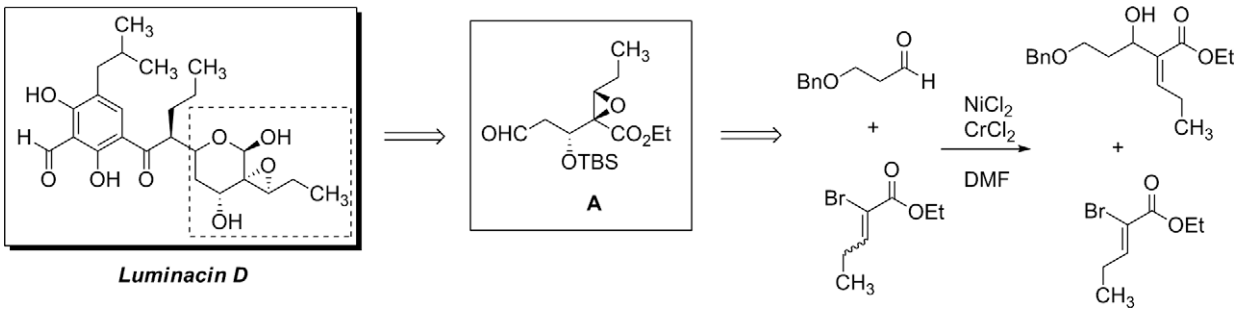
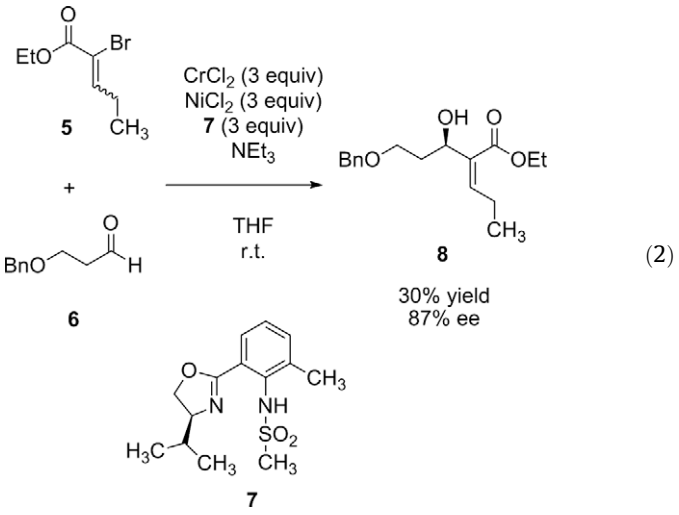


Scheme 1. Application of a Ni–Cr-mediated coupling to prepare a Baylis–Hillman intermediate in the synthesis of Luminacin D.

excess proving that the adjacent ester functionality does not impede the reaction (Eq. 2).[6,7] Interestingly, it was observed that the (*E*)-olefin isomer of acrylate **5** was the predominant reactive partner under the coupling conditions.[8] Presumably, this discrimination could be due to the lower reactivity of the (*Z*)-isomer from a more sterically encumbered nickel or chromium species with the ethyl substituent. Encouraged by the reactivity and selectivity obtained for this protocol, we proceeded to determine if other solvents effected reaction reactivity or selectivity. In analogy to reaction condition screening by Kishi and co-workers, acetonitrile was used as an alternate solvent. It was found that for aldehyde **6**, both THF and acetonitrile provided adduct **8** in comparable yield and enantiomeric excess.

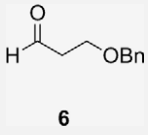
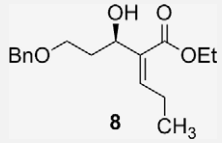
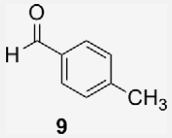
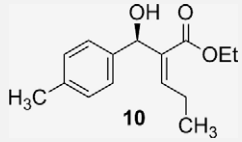
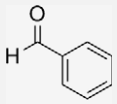
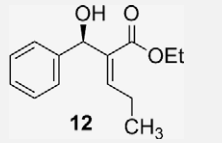
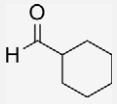
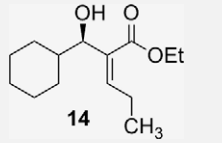
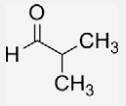
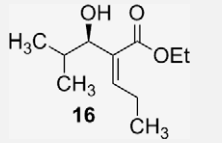
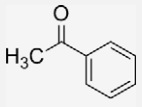
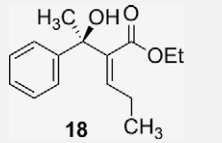


(2)

With these conditions in hand, we wanted to further explore what scope of electrophiles would perform favorably in this reaction. We were delighted to find that several aldehydes examined afforded selectivity under the nickel–chromium conditions (Table 1).[9] Analagous to aldehyde **6** (entry 1), aromatic aldehydes provided excellent selectivities in this reaction. *p*-Tolualdehyde **9** and benzaldehyde **11** (entries 2 and 3) furnished the desired Baylis–Hillman adducts **10** and **12** in fair yields (46% and 28%, respectively) and in excellent enantiomeric excess (90% and 94%, respectively). While aromatic aldehydes furnished selectivities >90%, we also discovered that other aliphatic aldehydes produced fair to good selectivities as well. Cyclohexanecarboxaldehyde **13** (entry 4) and isobutyraldehyde **15** (entry 5) afforded the Baylis–Hillman products **14** and **16** in 32% and 65% yield and 55% and 88% ee, respectively. In an attempt to generate tertiary alcohols, acetophenone **17** was also screened. However, it was found that this substrate was inert to the reaction conditions even under prolonged reaction times.

In conclusion, we have shown that substituted Baylis–Hillman adducts can be generated via an asymmetric nickel–chromium reaction with high enantiomeric excess (up to 94% ee). Both aromatic and aliphatic electrophiles are compatible with the reaction conditions and afford products in fair to moderate yields. Using such a strategy, it can be envisioned that substrates which would not be compatible under a traditional Baylis–Hillman type mechanism could also be made accessible by this methodology. Such experiments and future optimization toward a catalytic process are for future investigation.

Table 1
Substrate scope for coupling reaction[a]

Entry	Electrophile	Product	Yield[b] (%)	ee[c] (%)
1	 **6**	 **8**	30	87
2	 **9**	 **10**	46	90
3	 **11**	 **12**	28	94
4[d]	 **13**	 **14**	32	55
5[d]	 **15**	 **16**	65	88
6	 **17**	 **18**	N.R.	

[a] Reactions were carried out at rt in THF (0.20 M in aldehyde) using **5** (3.0 equiv as a mixture of olefin isomers) and (1.0 equiv) in the presence of $CrCl_2$ (3 equiv), $NiCl_2$ (3 equiv), and ligand **7** (3 equiv).
[b] Isolated yield after silica gel chromatography.
[c] Determined by HPLC using a chiral column.
[d] Four equivalents of vinyl bromide **5** was used.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.078.

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6. *Representative procedure for the synthesis of adduct* **8** *(note: all reagents were weighed out in a glove box)*: In a clean dry flask was weighed chiral ligand **7** (3 equiv). The ligand was dissolved in THF (concentration 0.17 g ligand/mL). After the ligand dissolved, $CrCl_2$ (3 equiv) was added to the solution. To form the chromium complex, Et_3N (3 equiv) was then added dropwise to the reaction mixture. To ensure complexation, the resulting solution requires a temperature of >30 °C. Slight warming might be necessary. The solution was then stirred for one hour turning dark green in color. Vinyl bromide **5** (3.0 equiv as mixture of olefin isomers) and aldehyde **6** (1 equiv) were then added to this solution. Finally, $NiCl_2$ (3 equiv) was added and the reaction mixture was diluted with THF (0.2 M in aldehyde). The solution was stirred at rt for 12 h. The mixture was cooled to 0 °C and ethylene diamine (10 equiv) was added dropwise and stirred for one hour. The reaction mixture was then diluted with heptane and water and stirred for 15 min. The reaction mixture was filtered over Celite, washed with heptane (50 mL) and water (50 mL), and transferred to a separatory funnel. The aqueous layer was extracted with heptane (3 × 10 mL) and the organic layer dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a crude green oil. The crude oil was then purified by silica gel chromatography eluting with heptane/CH_2Cl_2/MTBE (5/5/1). The Baylis–Hillman product was isolated as colorless clear oil and analyzed by chiral HPLC (Chiralcel OD for this particular substrate).
7. (a) *Characterization for compound* **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H, $OCH_2C_6H_5$), 6.21 (dt, 1H, J = 7.33 Hz, 0.88 Hz, $HCCCO_2Et$), 4.55 (m, 1H, CH_2CHOH), 4.52 (s, 2H, OCH_2Ar), 4.23 (q, 2H, J = 7.33 Hz, 7.03 Hz, $CO_2CH_2CH_3$), 3.65 (m, 2H, CH_2CH_2OBn), 3.45 (d, 1H, J = 5.86 Hz, OH), 2.45 (apparent quintet, 2H, J = 7.6 Hz, $CH_3CH_2CHCCO_2Et$), 1.95 (m, 2H, CH_2CH_2CHOH), 1.31 (t, 3H, J = 7.33 Hz, OCH_2CH_3), 1.05 (t, 3H, J = 7.61 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 143.9, 138.2, 133.2, 128.7, 128.0, 127.9, 73.5, 72.3, 68.7, 60.5, 36.4, 23.0, 14.5, 14.0; HRMS (CI) exact mass calcd for $[M+Na]^+$ ($C_{17}H_{24}O_4$) requires m/z 310.2018, found m/z 310.2015; $[\alpha]_D^{23.8} = +6.2$ (c 0.30 g/mL, CH_2Cl_2) (b) see Ref. 9.
8. We have not isolated any of the products related to coupling of the (*Z*)-bromoacrylate.
9. The indicated stereochemical outcome is consistent with that observed in Refs. 5a,b since the transition state for this coupling process is expected to be the same.