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A post aza Baylis–Hillman/Heck coupling approach towards the synthesis of constrained scaffolds

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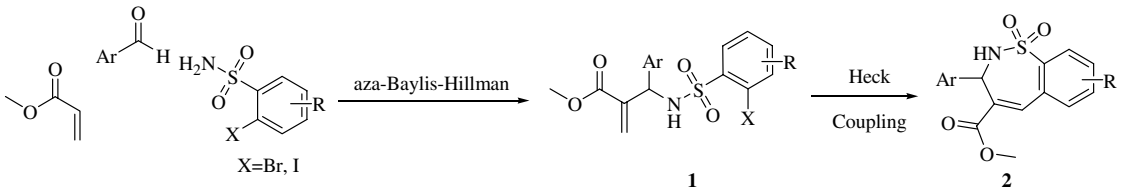
Abstract—An intramolecular Heck coupling of the product of an aza Baylis–Hillman reaction to afford conformationally constrained scaffolds is reported.

The Baylis–Hillman reaction, which involves the reaction between a Michael acceptor and an aldehyde to form highly functionalized α-methylene-β-hydroxy carbonyl compounds, has been studied extensively.[1] The corresponding aza version, which involves the reaction of a Michael acceptor with an imine as the electrophile, provides a convenient method for the synthesis of α-methylene-β-amino carbonyl compounds. This protocol produces the desired compounds in a single reaction step, although the aldimine usually needs to be preformed and isolated prior to the coupling reaction. Recently, Balan and Adolfsson have reported an efficient and selective one-pot three-component procedure for the formation of α-methylene-β-amino acid derivatives using the aza Baylis–Hillman protocol.[2] Nucleophilic, sterically nonhindered tertiary amines showed best activity as catalysts, and molecular sieves improved chemical yields and reaction rates.

We have been interested in the modifications of products of multi-component reactions to produce diverse collections of conformational constrained compounds.[3] Along these lines, we envisioned that the use of an *ortho* halo substituted sulfonamide or aldehyde component in the aza Baylis–Hillman reaction would afford a substrate for an intramolecular Heck coupling to afford bicyclic scaffolds **2** and **4** (Schemes 1 and 2).[4]

Initial attempts were directed towards the synthesis of the aza Baylis–Hillman adducts **1** and **3**. A competing reaction in the synthesis of these products is the formation of the Baylis–Hillman products. After considerable experimentation, it was found that using titanium isopropoxide, 2-hydroxyquinuclidine and molecular sieves in *i*-PrOH afforded respectable yields of the desired aza Baylis–Hillman products[2b] (Table 1). Preformation of the aldimine followed by the addition of the acrylate did not result in improved yields of the aza Baylis–Hillman products.

With the aza Baylis–Hillman products in hand, attempts to identify suitable conditions for the Heck coupling



Scheme 1. General scheme for an aza Baylis–Hillman/Heck coupling using a suitably substituted sulfonamide.

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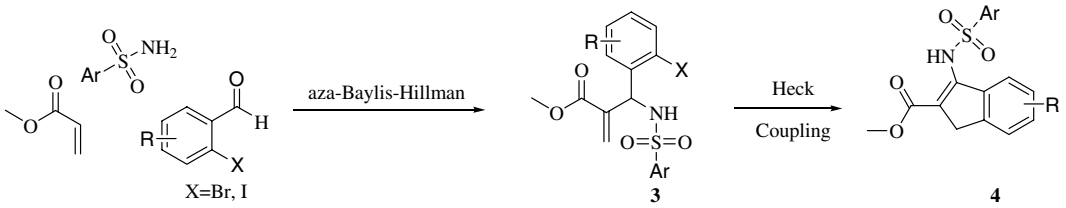
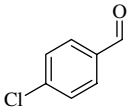
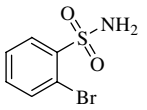
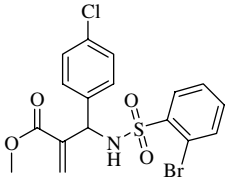
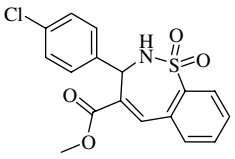
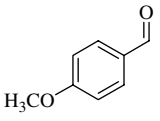
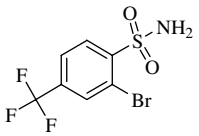
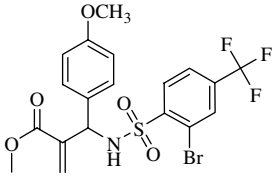
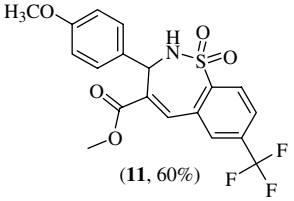
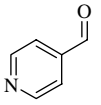
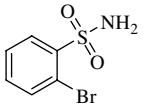
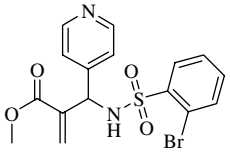
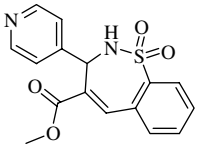
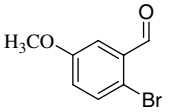
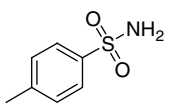
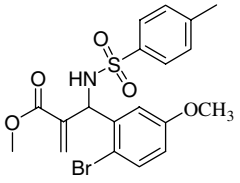
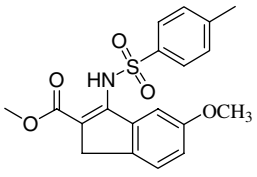
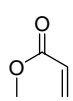
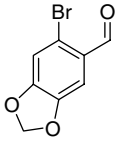
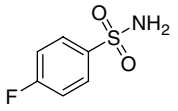
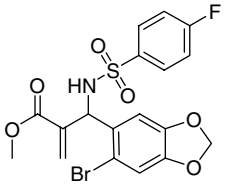
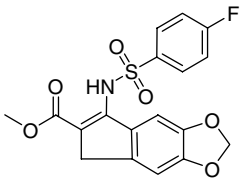
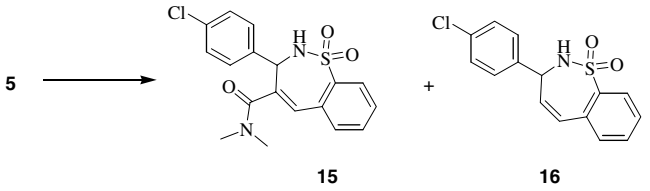


Scheme 2. General scheme for an aza Baylis–Hillman/Heck coupling using a suitably substituted aldehyde.

Table 1. Products of the aza Baylis–Hillman (ABH) and Heck coupling

Alkene	Aldehyde	Sulfonamide	ABH Product	Heck Product
			 (**5**, 66%)	 (**10**, 52%)
			 (**6,** 62%)	 (**11**, 60%)
			 (**7**, 71%)	 (**12**, 45%)
			 (**8**, 74%)	 (**13**, 77%)
			 (**9**, 77%)	 (**14**, 50%)

were commenced. The utility of microwave irradiation to facilitate organometallic reactions has been reported extensively.[5] Our initial attempts commenced with the use of $Pd(Ph_3)_4$ and triethylamine at various temperatures and catalyst concentrations.[6] However, the predominant product observed was the dehalogenated aza Baylis–Hillman product. Switching to a $Pd(OAc)_2$/$P(o\text{-tolyl})_3$ catalytic system with triethylamine in



Scheme 3. Product composition of Heck coupling in *N*,*N*-DMF.

DMF[7] afforded **15** and **16** in a 2:3 ratio, presumably formed from the generation of dimethylamine via thermal decomposition of *N*,*N*-DMF (Scheme 3).

Switching the solvent to THF eliminated the formation of **15** and **16**; however, the reaction had to be heated for 1 h to afford the desired product **10** in acceptable yields. Speculating that the slower reaction rate could be due to the sluggish heating profile of THF using microwave irradiation,[5] attempts to dope the reaction with varying amounts of polar solvents such as 1,2-dichlorobenzene and ionic liquids[8] were attempted. While the addition of 5% 1,2-dichlorobenzene afforded the desired product, the reaction time was not shortened. Doping THF with 5% of various ionic liquids, while significantly improving the heating profile, did not afford any of the desired product. Hence, the optimal conditions for the Heck coupling were to heat the aza Baylis–Hillman product, 5 mol % $Pd(OAc)_2$, 2 mol % P(*o*-tolyl)$_3$ and triethylamine in THF at 160 °C for 1 h.[9]

Aza Baylis–Hillman products obtained using *ortho* halobenzaldehydes were heated with $Pd(Ph_3)_4$ and triethylamine[6] in THF at 150 °C for 20 min to afford the conformationally constrained scaffolds **13** and **14**. Efforts to expand the diversity of scaffolds accessible via the products of the Baylis–Hillman reaction are ongoing and will be reported in the future.

Acknowledgements

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7. Smalley, T. L.; Mills, W. Y. J. *Heterocyclic Chem.* **2005**, *42*, 327.
8. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (c) The following ionic liquids were utilized in these experiments: 1-butyl-3-methylimidazolium chloride, 1-ethyl-3-methylimidazolium trifluoromethanesulfonate, 1-butyl-3-methylimidazolium tetrafluoroborate.
9. Representative protocol for the intramolecular Heck coupling: A microwave vial was charged with the aza Baylis–Hillman adduct **8**, 50 mg (0.11 mmol), $Pd(Ph_3)_4$ (3 mol %) and triethylamine (3 equiv) in 2 ml THF, sealed and heated at 150 °C for 20 min. The reaction mixture was diluted with 10 ml water and the crude product extracted with 20 ml ethylacetate and chromatographed to afford the desired Heck product **13** (31.5 mg, 77%). ^{1}H NMR (DMSO-d_6): δ 9.95 (br s, 1H, N*H*), 7.62 (d, 2H), 7.37 (m, 3H), 7.27 (d, 1H), 6.97 (dd, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 3.52 (s, 2H), 2.35 (s, 3H). MS (ESI) (*m*/*z*) 374 (M+H), 372 (M−H).