Enantioselective Organocatalytic Cyclopropanations. The Identification of a New Class of Iminium Catalyst Based upon Directed Electrostatic Activation

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With representation in more than 4000 natural isolates and 100 therapeutic agents, the cyclopropane motif has long been established as a valuable platform for the development of new asymmetric technologies. Within the realm of metal catalysis, cyclopropane formation has been accomplished using a vast array of organometallic carbenoids, while asymmetric organocatalytic cyclopropanations using catalyst-bound ylides have been pioneered by Aggarwal and Gaunt. Surprisingly, however, enantioselective cyclopropanation based upon the activation of olefin substrates has yet to be accomplished with either metal or organic catalysts.

Having established the capacity of chiral amines to catalyze a wide variety of asymmetric transformations using unsaturated aldehydes, we recently sought to extend this olefin-activation platform to the production of three-membered carbocyclic rings. In this context, we outline a highly efficient protocol for the construction of enantioenriched cyclopropanes using stabilized ylides with dihydroindole catalysts. As part of these studies we also propose a new stereoinduction concept for organocatalysis that we term directed electrostatic activation.

In 1965, E. J. Corey described the propensity of stabilized ylides to participate in cyclopropanation in lieu of epoxidation with amphiphilic electrophiles such as α,β-unsaturated aldehydes and ketones. With this chemoselectivity profile in mind, we initiated our enal-cyclopropanation studies with dimethylphenylacetyl sulfonyl ylide 1 and a variety of chiral amine catalysts (eq 1). Given the capacity of imidazolidinones to catalyze a diverse range of hydrogenation and conjugate addition reactions, we were disappointed to find that the iminium species derived from catalysts 2 and 3 were inert to the ylide 1 (0% conversion). To our further surprise, the use of catalytic proline provided good levels of reaction efficiency (72% conversion) albeit with moderate enantiocontrol (46% ee). In an effort to reconcile these atypical reactivity patterns, we developed a mechanistic postulate based upon the concept of directed electrostatic activation (DEA). Specifically, we rationalized that the proline-derived iminium 5 and the ylide 1 might readily engage in electrostatic association via their pendant carboxylate and thionium substituents. In doing so, the ylide carbanion and the iminium β-carbon would be transiently activated while in close proximity, thereby facilitating carbon–carbon bond formation. Furthermore, we assume that the zwitterion 5 can readily populate both E and Z iminium isomers, a configurational equilibrium that typically leads to diminished enantiocontrol (eq 2). Consistent with our observations, iminium systems derived from imidazolidinones 2 and 3 are electronically averse to thionium association and as such are unable to participate in this electrostatic activation.

Within this mechanistic framework, we rationalized that 2-carboxylic acid dihydroindole 6 might function as a useful DEA cyclopropanation catalyst. Specifically, we anticipated that the catalyst-derived zwitterion 7 would predominately populate the (Z)-iminium isomer to minimize van der Waals interactions between the substrate olefin and the aryl hydrogen. As a result, the carboxylate group on the catalyst framework would direct ylide addition selectively to the Re face of the activated olefin, thereby ensuring enantiocontrol (eq 3). As revealed in eq 4, this catalyst design plan was successful to furnish the accordant cyclopropane with excellent levels of induction (94% ee) and reaction efficiency (78% conversion).
Experiments that probe the scope of this new organocatalytic ylide cyclopropanation are summarized in Table 1. Significant latitude in the steric demands of the α,β-unsaturated aldehyde component is possible (entries 1–6, R₁ = Me, Pr, i-Bu, Ph; dr > 19:1, 89–96% ee). Moreover, high levels of asymmetric induction are available with enals that do not readily participate in iminium formation (entry 2, R₁ = CH₂OAllyl, 77% yield, 91% ee), as well as aldehydes that provide stable iminium intermediates (entry 5, R₁ = Ph, 73% yield, 89% ee). Structural variation in the ketone ylide component can also be realized (Table 1). The electronic nature of the aryl ring of phenylacyl ylides has apparently little influence on the stereochemical outcome (entries 1, 7, and 8, 92–96% ee). Moreover, sterically encumbered ylides are readily tolerated (entry 9, R₁ = COtBu, 95% ee).

We next performed experiments to test the validity of the proposed DEA mechanism (Scheme 1). The observation that this cyclopropanation can be conducted with enals but not electron-deficient olefins, such as unsaturated nitrile, nitro, or alkylidene malonate systems, lends support for an iminium-mediated pathway (eq 5). Moreover, N-methylation of the carboxylic dihydroindole framework, a step that removes the possibility of iminium formation, leads to a complete loss of catalytic activity (see catalyst 8). We have also found a trend toward increased rates and enantiocontrol as the polarity of the solvent is decreased. These results are consistent with the proposed DEA mechanism wherein substrate activation and ζ-facial delivery are accelerated by ionic interactions between the ylide and catalyst without substrate stabilization by the reaction medium. Furthermore, O-methylation of the carboxylic dihydroindole is found to suppress catalyst function (see catalyst 9), again consistent with the need for a zwitterionic iminium. Last, the sense of asymmetric induction observed in all cases was anticipated by this electrostatic model.

Table 1. Scope of Organocatalytic Ylide-Cyclopropanation

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>product</th>
<th>% yield</th>
<th>dr</th>
<th>ee</th>
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<tr>
<td>1</td>
<td>Propyl</td>
<td>COPh</td>
<td>85</td>
<td>30:1</td>
<td>95</td>
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</tr>
<tr>
<td>2</td>
<td>CH₂OAllyl</td>
<td>COPh</td>
<td>77</td>
<td>21:1</td>
<td>91</td>
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</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>COPh</td>
<td>67</td>
<td>&gt;19:1</td>
<td>90</td>
<td></td>
</tr>
<tr>
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<td>CH₂OAllyl</td>
<td>COPh</td>
<td>74</td>
<td>24:1</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>COPh</td>
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<td>33:1</td>
<td>89</td>
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</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Me</td>
<td>63</td>
<td>43:1</td>
<td>96</td>
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</tr>
<tr>
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<td>Propyl</td>
<td>COPh-Brom</td>
<td>67</td>
<td>72:1</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Propyl</td>
<td>COPh-OMe</td>
<td>64</td>
<td>&gt;11:1</td>
<td>93</td>
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<tr>
<td>9</td>
<td>Propyl</td>
<td>COtBu</td>
<td>82</td>
<td>6:1</td>
<td>95</td>
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</tbody>
</table>

Scheme 1. Evidence for Proposed DEA Mechanism

* Diastereoselectivity determined by GLC or 1H NMR analysis. determined by chiral GLC analysis. Reaction was conducted at 4 °C.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a superb review on stereoselective cyclopropanations, see: Lebel, H.; Marcoux, J. F.; Molinario, C.; Charette, A. B. Chem. Rev. 2003, 103, 977.
(8) Proline is typically a poor catalyst for iminium-activated processes.
(9) Entry 1 has been performed on a 1 mmol scale (88% yield, 95% ee).

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