Phthalide Synthesis

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Catalytic Intramolecular Ketone Hydroacylation: Enantioselective Synthesis of Phthalides

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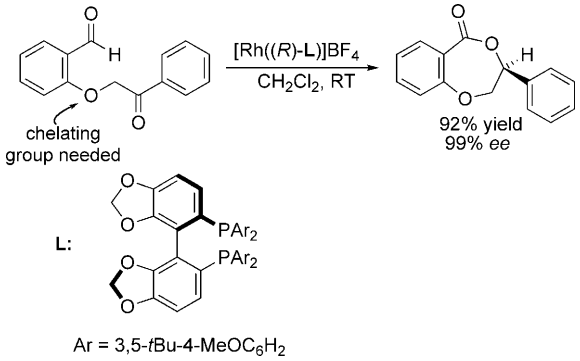
The development of a new transition-metal-catalyzed transformation can often allow a traditional reaction, perhaps one that employs stoichiometric amounts of reagents and harsh reaction conditions, to be replaced by a selective, atom economic process which proceeds under mild reaction conditions. This is certainly the case with the recent report from Dong and co-workers of a catalytic enantioselective synthesis of phthalide compounds.[1] The disproportionation of aldehydes has traditionally been achieved under basic conditions and is known as the Cannizzaro reaction.[2] A Lewis acid promoted variant—the Tishchenko reaction—is a related transformation that converts two carbonyl units into the corresponding ester.[3] Both processes suffer from the formation of side products and have not been readily adapted to catalytic asymmetric reactions.[4] As an alternative to these processes the Dong research group has developed catalytic enantioselective intramolecular ketone hydroacylation reactions.[1,5]

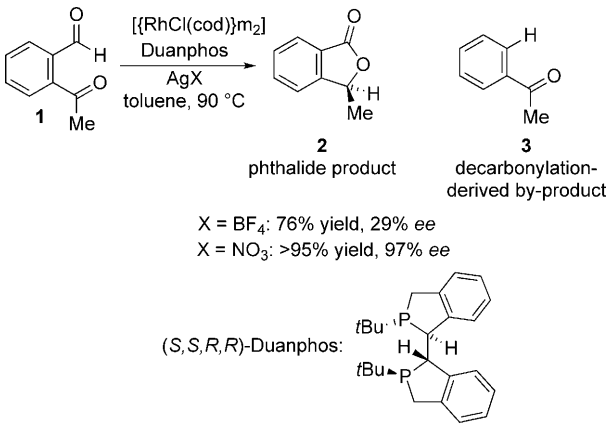
Transition-metal-catalyzed hydroacylation reactions usually proceed through initial formation of an acyl metal hydride species, and subsequent addition of this species across a multiple bond. Hydroacylation reactions of alkenes and alkynes are now well-studied processes, with a number of enantioselective variants already reported.[6] However, the corresponding processes requiring addition of the acyl metal species across a ketone or an aldehyde—carbonyl hydroacylation—are much less studied.[7] The key intermediates for both types of reaction, the acyl metal hydride species, are formed by the oxidative addition of the metal catalyst to the aldehyde C–H bond; a process that can be considered as a type of C–H activation. In common with a number of reactions that are based on C–H functionalization, hydroacylation reactions offer advantages in terms of step and atom economy.

Dong and co-workers originally developed a catalytic enantioselective intramolecular ketone hydroacylation reaction as a route to enantiomerically enriched seven-membered lactones (Scheme 1).[5] To achieve efficient reactions the substrates employed in these transformations were required to feature a chelating ether group. Developing a ketone hydroacylation route to phthalide compounds presented a greater challenge, as the substrates needed to target the phthalide architecture would no longer allow the presence of a coordinating ether group.



Scheme 1. Synthesis of seven-membered lactone derivatives based on enantioselective ketone hydroacylation.

The reaction shown in Scheme 2 illustrates the basic process used to access enantiomerically enriched phthalide compounds. Ketobenzaldehydes such as **1** were the key substrates for the process, and delivered five-membered lactones **2**, phthalides, through the proposed ketone hydro-



Scheme 2. Enantioselective formation of phthalides; cod = cycloocta-1,5-diene.

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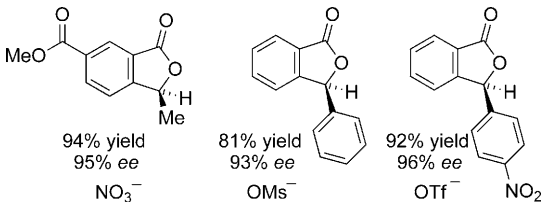
acylation reaction. As with the majority of transition-metal-catalyzed hydroacylation reactions the formation of by-products originating from decarbonylation, in this case ketone **3**, was a competing process. After evaluating a variety of ligands, solvents, and counterions, the combination of $[\{RhCl(cod)\}_2]$, the phosphine ligand (*S*,*S*,*R*,*R*)-Duanphos, toluene, and a nitrate counterion were found to be optimal. Using this combination of reagents, phthalide **2** was obtained in 95% yield with an enantiomeric excess of 97%; crucially, only a trace of the decarbonylation-derived by-product **3** was observed. Interestingly, the optimization process revealed a significant dependency on the nature of the counterion.[8] For example, when ketoaldehyde **1** was subjected to identical reaction conditions but the counterion was changed from NO_3^- to BF_4^-, the phthalide product was obtained in a lower 76% yield and with a poor *ee* value of 29%. In addition 24% of the decarbonylation product was also obtained. In general, more-coordinating counterions were found to deliver higher enantioselectivities. However, a cationic complex was still needed to obtain a reactive catalyst; for example, when using a Cl^- counterion a high enantioselectivity was maintained (97% *ee*), but the reaction required 3 days to reach completion (compared to 7 h with the NO_3 system). The choice of the nitrate counterion provided the authors with the optimal balance of reactivity and selectivity.

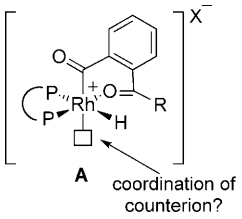
Dong and co-workers utilized the optimized reaction conditions to probe the scope of the process. Substitution of the aromatic backbone was tolerated well and an impressive range of both electron-donating and electron-withdrawing groups could be included in the majority of positions around the ring. The exception was the position immediately adjacent to the ketone group; presumably steric interactions from this position limited reactivity. Variation of the ketone substituent was also explored. Given the close proximity of the ketone substituent to the site of reactivity, it was perhaps not surprising that larger substituents resulted in slower reactions. For example, exchanging the substituent from methyl to ethyl groups increased the reaction time from one to two and a half days (using 5 mol% catalyst). Nevertheless, a number of aryl groups could also be included; Scheme 3 shows two examples



Scheme 3. Examples of substituted, enantioenriched phthalide products obtained using the basic process shown in Scheme 2, together with the counterion used with each example.

together with an ester-substituted product. While exploring variations of the ketone substituents the authors again found a significant counterion dependency and to obtain optimal yields and enantioselectivities for particular substrates a number of counterions were explored, showing that nitrate, mesylate, and triflate counterions all deliver effective systems with certain substrates.

Phthalide compounds are valuable products, they display a range of biological activities, and the catalytic enantioselective synthesis described by the Dong group certainly delivers an efficient and highly selective route to these valuable targets. The authors propose complex **A**, which features a vacant coordination site, as an intermediate en route to the phthalide products. The considerable counterion dependence discovered during the optimization and scope studies fits well with the proposed model. The fact that the counterion has been shown to play such a major role in controlling the reaction pathway and the enantioselectivity of the process, significantly, with the more-coordinating counterions delivering the most selective reactions, suggests that counterion engineering may offer further opportunities for reaction discovery. For example, could a chiral, enantiomerically enriched counterion be partnered with an achiral phosphine ligand to deliver an enantioselective process?[9] Further opportunities for extension of this chemistry could include the development of ketimine hydroacylation reactions, which would potentially allow a route to enantiomerically enriched lactam derivatives.



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