Ethylene Glycol Assisted Intermolecular Pauson–Khand Reaction

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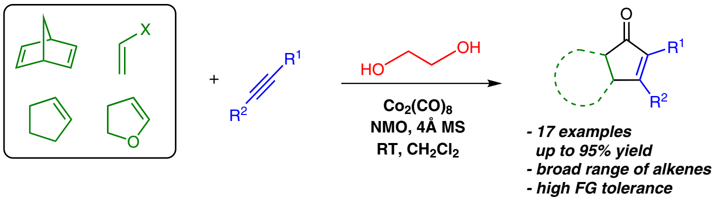

2–4 fold increased yields of PKR with unstrained alkenes

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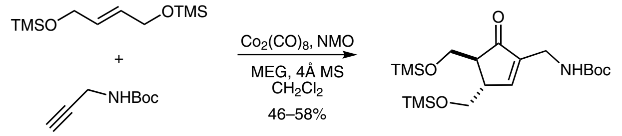
Abstract The use of ethylene glycol as additive in the *N*-oxide-promoted intermolecular Pauson–Khand reaction (PKR) has been studied. The addition of 15% ethylene glycol to the reaction mixture consistently increased (from 20% up to 2–4-fold) the reaction yields.

Key words Pauson–Khand reaction, cobalt, ethylene glycol, cyclopentenones, cycloaddition

The Pauson–Khand reaction (PKR)[1] is one of the few direct methods to synthesize five-membered ring carbocycles from acyclic precursors. When executed in an intramolecular fashion, this cobalt-mediated [2+2+1] cyclization is an extremely efficient way to build up complex cyclopentane polycycles.[1,2] The intermolecular PKR has found more limited use due to the narrow scope of the alkene. In fact, only strained olefins, such as norbornadiene or cyclopropene[3] or highly unhindered alkenes such as ethylene[4] gave high yields. However, the intermolecular version has a great potential since it allows cyclopentenones to be built up from very simple starting materials, namely an alkene, an alkyne, and carbon monoxide.[5]

During recent decades, much effort has been devoted to enhance the yields of this reaction using a variety of promoters or additives.[6] In 1990, Schreiber and co-workers discovered that the PKR, which was typically performed at high temperatures (60–110 °C), could also be promoted using *N*-oxides[7] such as *N*-methylmorpholine-*N*-oxide (NMO) in dichloromethane.[8] These conditions allowed the reaction to take place at room temperature and often gave better yields.[9]

In 2011, Baran and co-workers reported the total syntheses of (±)-axinellamines A and B.[10] The starting material of these synthesis was a cyclopentenone prepared by an intermolecular PKR using 1,4-bis[(trimethylsilyl)oxy]but-2-ene (Scheme 1). The success of the PKR with this unstrained olefin was possible only when using NMO as promoter and adding monoethylene glycol (MEG)[11] and 4 Å molecular sieves (MS) to the reaction. Under these conditions, a remarkable 46–58% yield was obtained (without MEG, yields dropped to 15–25%). Although Baran and co-workers stated that ethylene glycol was an essential additive, to the best of our knowledge, these conditions have not been used in any other PKR reported to date. We envisioned that, using this novel methodology, other olefins might give better yields and therefore a wider range of alkenes could be used.



Scheme 1 Ethylene glycol assisted intermolecular PKR used in Baran's synthesis of axinellamines

Here, we studied the role that ethylene glycol displays in the stoichiometric *N*-oxide-promoted intermolecular PKR. The effect of Baran's conditions was tested when performing the reaction with strained alkenes such as norbornadiene, poorly reactive cyclopentenes,[12] and several ethylene synthetic equivalents.[13]

The new protocol was tested first with norbornadiene (NBD), which is the most relevant alkene substrate in intermolecular PKR. We observed that in all cases, the yields using ethylene glycol and molecular sieves as additives were substantially higher (Table 1, entries 2, 4, 6, and 8). The reaction is usually stereoselective affording the *exo*-adduct as the major stereoisomer. In the case of the reactions with ethylene glycol, the stereoselectivity towards the *exo* further increased slightly. The presence of ethylene glycol low-