Cyclic diguanylate (c-di-GMP) is a bacterial second messenger that controls multiple processes. Most c-di-GMP networks have dozens of diguanylate cyclases (DGCs) that cyclize c-di-GMP. These networks appear highly organized whereby a DGC signals a specific cellular function, despite simultaneously producing the same small molecule as its sibling DGCs. For this system to have order, mechanism(s) must exist that allow DGCs to specifically signal their targets. Although it has been speculated physical interaction provides specificity, there is scant evidence of how such specificity is achieved. Our results show a DGC interacting with its target protein at a conserved barcode-reader interface, and this interface can be predictive of DGC-target protein interactions. We also show this interaction depends on c-di-GMP binding the DGC's inhibitory site, thus likely quieting the enzyme's catalytic activity while signaling its target and effectively eliminating cross-talk among unrelated members of the network.